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TITLE: BRAVEMIND: Advancing the Virtual Iraq/Afghanistan PTSD Exposure Therapy for MST

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14. ABSTRACT

PTSD can result from exposure to actual or threatened death, serious injury or sexual violation. Military Sexual Trauma (MST) has been recognized as a significant risk factor for the development of PTSD. This has become an issue of grave concern within the military, as reports of sexual violations and assaults have been on the rise over the last ten years, and have garnered significant popular media attention. This project developed content for inclusion in the BRAVEMIND virtual reality exposure therapy (VRET) system that provided new customizable options for persons who have experienced MST and ran a pilot study with a target sample of 20 persons diagnosed with PTSD due to MST. The effort in the second year focused on enrollment and treatment of subjects for the study. A no-cost extension was granted for one year until May 26, 2017 to allow completion of the study.

15. SUBJECT TERMS

PTSD, Virtual Reality, Prolonged Exposure, Military Sexual Trauma

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1. INTRODUCTION

PTSD can result from exposure to actual or threatened death, serious injury or sexual violation. This is of particular relevance for Service Members (SMs) who may face trauma from both the threat that is naturally inherent in the combat theatre, as well as from the possible additive occurrence of sexual violations from within the ranks. Thus, military sexual trauma (MST) that is experienced as a threat or result of an occurrence of a sexual violation/assault within a military context can produce additional risk for the development of PTSD in a population that is already at high risk due to the existing occupational hazards present in the combat environment. A report issued by the Joint Chiefs, together with the DoD Sexual Assault Prevention and Response Program (SAPR) (DoD, 2012), specifies the need for improvements in, "…advocacy coordination, medical services, legal support and (behavioral health) counseling for the victim" (p. 13). This has become an issue of grave concern within the military, as reports of sexual violations and assaults have not only been on the rise over the last ten years, but have also garnered significant popular media attention. Overall, 6.1% of women and 1.2% of men (active duty SMs) indicated they experienced unwanted sexual contact in 2012. For women, this rate is statistically significantly higher in 2012 than in 2010 (6.1% vs. 4.4%) (DoD, 2012). A bleaker picture of the problem emerges when reports from post-discharge Veteran surveys are considered. In a nationwide randomly selected sample of women seeking care through VA medical centers, approximately one out of four reported experiencing a sexual trauma while on active duty (Skinner et al., 2000). The reported prevalence rates of MST in women were 20-25% for sexual assault and 24-60% for sexual harassment. Thus, while the DoD is mobilizing to reduce the incidence of MST with novel education and prevention programs, significant effort is also required to develop and disseminate effective treatments to address the existing problem of PTSD due to MST. The major goals of this project were to create VR content to extend our VR PTSD Exposure Therapy system to address the clinical needs of those with PTSD due to Military Sexual Trauma and to test the efficacy of the system in a pilot clinical trial. The system will not recreate a sexual assault, but rather, sets up the contexts surrounding the assault in which users can be supported in the therapeutic confrontation and processing of MST memories in accordance with the protocol that has been used previously that implements PE within the simulations (Rothbaum et al., 2008).

2. KEYWORDS

- PTSD, Virtual Reality, Prolonged Exposure, Military Sexual Trauma

3. ACCOMPLISHMENTS

- **What were the major goals of the project?**
  - Specific Aim 1 – To extend and evolve the BRAVEMIND (BM) system to enhance the relevance, functionality, and usability of a VRET system for persons with PTSD due to MST.
  - Specific Aim 2: We will test the clinical efficacy of the VRET system in an initial safety, feasibility and waitlist clinical trial of 20 users diagnosed with PTSD due to MST.
- **What was accomplished under these goals?**
  - **Specific Aim 1, Major Task 1 – Develop Working MST VRET System for Study**
    All of the below Subtasks were completed and the system was delivered to the clinical site at Emory University in Mid-February 2015.
    - **Subtask 1: Review existing feedback and collect and organize new feedback from patients, clinicians, and consultants on MST contexts for design input.**
      This was the initial step where our subject matter experts (SMEs) consultants, Barbara Rothbaum, JoAnn Difede and Chris Reist participated in conference calls that explored and discussed the possible desired VR contexts and functionalities that would be useful for this application. This input drew from their previous clinical expertise in both treatment and research in the area of civilian sexual trauma. The biggest concern involved finding the best balance between what the

budget would support and the creation of content that would provide the widest range of exposure contexts needed to address the diverse experiences that MST victims present with. This was an iterative process that involved frequent and regular email and phone conversations between ICT and the SMEs. As well, the initial design was further informed by a review of key literature ranging from government reports (cf. DoD Sexual Assault Prevention and Response Program (SAPR) (DoD, 2012)) to comprehensive journalism reports that provided great detail on the sexual trauma experiences of those in the military (cf. Moffeit & Herdy, 2004). These inputs formed the basis for the design work in Subtask 2.

- **Subtask 2: Design and specify settings, stimuli and features based on input.** From the results of Subtask 1, the team (ICT and SMEs) determined that since most MST occurs on or around US military bases, we would need to create a significant amount of US civilian contexts and relevant trigger stimulus input functionality. It was also determined that some of the existing BRAVEMIND (BM) Iraq/Afghanistan content could be reused as developed initially (when the contexts were relevant to the user's experience of MST—for example, in abandoned buildings, vehicles, outdoor spaces, etc.), but that the remote Forward Operating Base scenario was most ideally suited as a context, that with modification, would provide the best setting for spending resources to evolve specific communal, shared space areas—the types of areas where in-theatre MST has often been reported to occur. Thus, multiple MST scenarios were agreed upon and designed: 1) a remote Forward Operating Base that had shared barrack areas, primitive sheltered offices, remote outdoor spaces, shower areas, and latrines. And, 2) a US Base and Small Town scenario that included a bar area, back lots, alleys, streets, strip mall, motel, and a car/taxi ride. Other related US Base scenes were designed that included: apartment and motel bedrooms/bathrooms/living spaces, a land-based office and a shipboard office. A wide range of indwelling functionality was designed in collaboration with the clinical partners such as: the user experience of walking and laying down, ambient lighting controls, perpetrator customization and behavior, car ride controls, and the creation of a diverse range of audio trigger stimuli clips relevant to the VR scenarios and contexts.

- **Subtask 3: Design and develop extended BRAVEMIND (BM) functionality as needed.** All of these elements of the design were iteratively evolved over the first year of the project where the clinical team could examine early prototype builds and provide input on the layout, lighting, and content in the scenarios as they had the opportunity to review evolving instances of content development via video and still image captures, in addition to initial compiled versions of the VR simulation sections and prototype as they became available. See **Figure 1** for example images of some of the content developed for the VR MST scenarios.

- **Subtask 4: Produce needed art and related assets.** This occurred in parallel with Subtask 3 and it was the task of the ICT art and development group. Daily meetings were held to review the status of art creation and critiques of various iterations of the art by the team. The rough structure of a remote Forward Operating Base had been previously created, but required additive art assets to expand the content and functionality for MST relevance. A completely new set of contextual 3D art was required to create the US Base and Small town civilian-themed scenario.

- **Subtask 5: Integration of assets into BRAVEMIND (BM) system.** As the art assets were created for both scenarios, all team members (ICT and SMEs) provided feedback on the graphic art appearance/quality and upon consensual approval, the art (and necessary functionality to present the art and events) was integrated into

the BM software architecture. The architecture consisted of the actual simulated VR worlds AND a clinical "wizard of oz" type interface. This point and click clinical interface is the control panel that clinicians use to select scenarios, place users in strategic locations within the scenarios, adjust ambient atmospheric, weather, lighting, and audio settings, in addition to the introduction of strategic trigger stimuli, all within the standard clinical protocol for appropriately delivering VRET (note—the VRET therapy process is detailed in the original proposal). Layout of the controls of the interface was based on the template created from the original BM combat-related PTSD VRET system (user-tested for usability) with slight modifications for the delivery of content unique to the MST system (e.g. Perpetrator appearance and behavior customization controls, individual room lighting effects, door controls, etc.). **Figures 2 and 3** present the front end interface layout for both major scenario components.

- **Subtask 6: Bug test Q&A.** After the scenarios were integrated into the BM architecture, Q&A and bug testing occurred internally at ICT in order to deliver an optimized and usable system to the clinical SME group for a final round of iterative feedback. The Q&A was completed by early December 2014 and was then sent out to the clinical SMEs for their feedback that would then be used to inform the creation of the final deliverable system to be used in the clinical trial in the next phase of the project. Although this was delivered right before the hectic time of the holiday season, the clinical SMEs tested the system over the next month and returned their feedback to us in January of 2015. Due to the tight collaboration that ICT and the SMEs had going on throughout the early design and development process, with numerous cycles of iterative feedback, the issues reported to ICT for modification were relatively small and easily addressed. One example of this involved the addition of a quick interface key to eliminate the presence of the perpetrator rapidly, as the "following perpetrator" function (where the character would follow the user wherever they navigated in the scenario, akin to the "Terminator" character in the classic Si-Fi movies) was deemed to be more provocative when actually implemented in the scenario than had been anticipated during the design phase. Clinical SMEs wanted the capability to instantly eliminate its presence to better pace the VRET process. Other examples included the addition of various sound effects such as the sound of door locks being shut in the car and sounds of zippers, heavy breathing, clothes being torn, were requested. As well, additional content that made the car experience more diverse and flexible was added. The setting for the car ride to have the additional option of emulating the back seat of a taxi was requested as well as the ability to put the user in either the front of back of the car and to easily add or take away the perpetrator from the front or back seat was also requested. All of the requested adjustments were implemented by ICT and another round of bug testing occurred, whereupon what turned out to be an acceptable and final deliverable system was made available to the clinical site. Upon approval of the system by the clinical team, the PI visited the clinical site at Emory to work with the clinical team to sort out any training or use issues as needed for the clinical use of the system. With the BRAVEMIND MST system delivered, the next major Specific Aim of the project could commence.

- **Specific Aim 2, Major Task 1 – Conduct Study**
  As of the end of the reporting period, all subtasks have been completed. Subtasks 1 and 2 were completed in the previous reporting period. Subtasks 3, 4, 5, and 6 were completed at the end of the current reporting period.
  - **Subtask 1: IRB and Administrative Approval Process**

- 07/14/2014—IRB granted approval upon minor corrections
- 08/05/2014—IRB approval granted following minor corrections
- 09/02/2014—IRB approved "sensitive study status"
- 10/13/2014—Amendment approval, including changes to informed consent form and changes to study team
- 12/03/2014—Amendment approval, including waiver of signature for phone screen content, Emory added as a study site, protocol update, oral consent form, and changes to informed consent
- 02/13/2015—Amendment approval, including change to informed consent, protocol, and application for NIMH Certificate of Confidentiality
- 03/05/2015—Amendment approval, including changes to study team and changes to recruitment materials (i.e., internet ad, MST clinician handout, MST flyer, and PTSD screen card)
- 03/19/2015—Emory declared designated IRB, on which USC will rely for review and continued oversight of human subjects research for this study
- 04/06/2015—Amendment approval, including changes to consent form, changes to study team, changes to protocol document, and changes to questionnaires and surveys (addition of SimSensei Questionnaire, removal of PCL-5 and PSSI-5)
- 04/13/2015—Amendment approval, including changes to study team, changes to protocol document, changes to informed consent, addition of Certificate of Confidentiality, changes to questionnaires (added PCL-5).
- 05/08/2016—Annual IRB approval
- 08/03/2016—Amendment approval, changing inclusion criteria so that participants are on a stable dose of psychotropic medications for 3 months instead of 2 months prior to study enrollment.
- 10/17/2016—Amendment approval, changing study from a randomized trial to an open trial by dropping the waitlist condition, eliminating the 6-week post randomization time point as it is no longer warranted given the request for changing the study to an open clinical trial. Adding an option to receive treatment sessions daily as part of the Emory Healthcare Veterans Program's 2-week Intensive Outpatient Program (IOP) (most participants are from out of state). Adding an option for participants to complete the 3-month follow-up remotely, via phone or email. Eliminating the $20 reimbursement for treatment sessions for IOP participants since Emory was already covering their lodging and food through a separate grant. Updating study team members on the protocol.
- 11/08/2016—Amendment approval, including changes to the informed consents which now more clearly define for study staff which informed consent to use, based upon whether the participant is in the Intensive Outpatient Program (IOP) or regular Outpatient Program (OP). Changes to oral consent for screening with better formatting and correcting the inclusion criteria that a participant must be on a stable medications for a minimum of 3 months, not 2 months, which is also reflected in the current protocol.
- 05/01/2017—Annual IRB approval

- **Subtask 2: Hire and Train Study Personnel.**
  Completed. All study personnel completed the web-based Collaborative IRB Training Initiative (CITI) Program in the Protection of Human Subjects in

Research. All investigators have completed training in Conflict of Interest and Key Concepts in Clinical Research for Investigators through the Emory University Office for Clinical Research. All study personnel received additional training specific to study roles, including training in obtaining informed consent and administering study assessments. On 2/17/2015, Emory initiated its study kickoff meeting. In attendance were all Emory and USC study team personnel. Recruitment, screening and enrollment procedures were outlined and reviewed and training was given for administering SimSensei. Psychophysiological data collection, which Dr. Rothbaum and her team collect for other studies, was outlined and reviewed as well. All therapists will have been trained in Prolonged Imaginal Exposure therapy (PE) followed by training in VRET, and will be supervised by psychologists experienced in providing VRET. Under the clinical guidance of Dr. Rothbaum, therapists and assessors receive weekly supervision. All treatment sessions are videotaped to ensure reliability.

- **Subtask 3: Subject Recruitment.**
  Participants were self-referred from advertisements, community outreach, mental health provider referrals, or through Emory Healthcare Veterans Program. Advertisements included flyers around the Atlanta area, radio and television coverage, postings on websites such as craigslist, and social media outreach through http://emoryhealthcare.org/veterans-program/index.html, Facebook, and Twitter. Veteran Outreach Coordinators actively engaged in outreach efforts by attending military/veteran events such as Veteran's Day functions, military family resource fairs, career fairs, Female Veterans and Active Duty Female Summit, VA Town Hall Meetings and other relevant events. Patients were referred from both VA personnel and non-VA sources. Procedures were established with the VA to ease the referral process between the VA and Emory.

  Phone screening was conducted by a member of the study team to determine appropriateness of this study for each participant and to inform the participant of study procedures. Basic inclusion and exclusion criteria, including psychological history, suicidality, and alcohol/substance abuse/dependence, and ability to wear VR headset were briefly reviewed according to a structured telephone screening interview. The investigators were granted an IRB waiver of documentation of consent/HIPAA authorization for the various pre-randomization screening activities, including the telephone screening process. By the end of the grant period, a total of 27 people were assessed for eligibility, with 22 being eligible for the study and 20 agreeing to participate in the study (see Appendix 2).

- **Subtask 4: Assessment of Participants (target n=20).**
  See Appendix 1 for a full review of assessment measures. Enrolled participants completed a pre-treatment assessment, 6-week post randomization assessment, post-treatment assessment if treatment continues beyond 6-week post randomization assessment, and a 3-month follow up assessment. Following the initial screen, an initial evaluation was scheduled for individuals that were potentially eligible and interested in participating. Potential subjects were asked to provide a copy of their DD214 to verify their military service record. Participants met with the study assessor who was trained in obtaining informed consent and all study assessments. The assessor discussed all study procedures with the subject and informed them that the research is sponsored by the DoD. They answered any questions the participants may have. The assessor determined if the participant had

the capacity to consent. To determine eligibility, participants were interviewed using the gold standard Clinician Administered PTSD Scale (CAPS-a structured clinical interview) and MINI assessments, to establish PTSD diagnosis and identify comorbid diagnoses. All assessments were conducted by independent assessors who were blinded to treatment condition.

Once a participant was determined to be eligible for the study, the assessor assigned them a study number. Each study number had a sealed envelope containing the randomized condition. At assignment on the day of the pre assessment visit, the assessor opened the envelope and informed the participant of their study group. They either scheduled the participant to begin therapy or for the post-waitlist assessment in six weeks. In addition to the information gathered for eligibility, participants also completed several other self-report and clinician administered measures as listed in Appendix 1. We collected a one-time 2mL saliva sample to be used for the purpose of DNA extraction. DNA extraction was optional and was presented to participants under a separate consent. Psychophysiological data was collected including 4 cortisol samples.

Due to the majority of participants completing treatment beyond the 6-week post-randomization date and only one waitlist-condition participant engaging in treatment, the study team determined the 6-week waitlist was not an effective comparison group and, as a result, was delaying treatment unnecessarily. With IRB approval granted on October 17, 2016, the research team amended the study protocol to shift the study from a randomized control trial to an open clinical trial (see Appendix 3, IRB Amendment 1). Consistent with this change, the six-week post-randomization assessment was removed from the study protocol, and psychophysiological assessment was added to the post-treatment assessment (see Appendix 3, IRB Amendment 2)

By the end of the grant period, a total of 15 participants completed the pre-assessment, 9 of whom were randomized to either waitlist or treatment conditions and 6 of whom were enrolled to start treatment immediately as part of the open clinical trial (see Appendix 1 and Appendix 3, Amendment 1 for further details).

- **Subtask 5: Treatment of Participants (target n=20).**
  Participants were randomized to receive VRET immediately or wait 6 weeks during which time they continued to receive usual care. Beginning October 17, 2016, all participants were enrolled to receive VRET immediately. VRET treatment was delivered in a minimum of 6 sessions and a maximum of 12 sessions, based upon reaching criterion of 70 % symptom improvement as indicated on the PCL-5 from baseline, or an agreement between clinician and participant that maximum treatment response has been achieved. All sessions were individual and weekly or twice weekly. Beginning October 17, 2016, participants were offered the opportunity to complete the MST treatment protocol through the Emory Healthcare Veterans Program Intensive Outpatient Program, which included 6-12 individual VRET sessions (see Appendix 3, IRB Amendment 3, 3a, 3b).

  Consistent with traditional Prolonged Exposure therapy, the first session was spent in information gathering, treatment planning, and explaining the treatment rationale to the patient. Information gathering consisted of reviewing the history of PTSD

and their military service and included a brief psychosocial history, including review of prior treatment. Additionally, a rationale for VRET was provided and breathing retraining was introduced and practiced in session. Session 2 reviewed common reactions to trauma, provided a rationale for in vivo exposure, and included construction of the hierarchy for in vivo exposure. VR exposure began in Session 3. The VRET sessions lasted 90-minutes each and consisted of 1) 15 minutes of checking in with the patient about their functioning and anxiety and homework completion since the last session, 2) up to 45 minutes of exposure to their traumatic memories and the virtual stimuli, followed by processing and discussion about the material from the exposure, and 3) homework assignment. During VRET sessions patients wore a head-mounted display with stereo earphones that provides visual and audio cues consistent with Iraq/Afghanistan forward operating base military scenarios or other US base-related scenarios or US civilian small town scenarios as appropriate for the individual patient. The therapist simultaneously viewed on a video monitor all of the virtual environments in which patients were interacting and therefore was able to comment appropriately and attempt to match stimuli that the patient described during their trauma narrative while immersed in the virtual scenarios. The therapist made appropriate comments and encouraged continued exposure until anxiety habituated. During exposure, information was gathered on the participant's anxiety level through the use of a 0-100 SUDs scale. As the number of sessions was limited, we limited exposure to the identified index trauma, and in some cases, a second traumatic event.

By the end of the grant period, a total of 9 participants completed the treatment phase.

- **Subtask 6: Follow-up Assessments (Post-Treatment/3-month Follow-up).** By the end of the grant period, 8 participants completed the follow up phase, including both the post-treatment and 3-month follow up assessments.

- **Subtask 7: Conclude Study Enrollment.** Study enrollment for the randomized control trial concluded on August 12, 2016 (n = 9). Enrollment for the open clinical trial concluded on 4/19/2017.

- **Subtask 8: Conclude 6 Week Post Randomization Assessments.** Completed post-treatment assessments and follow up phase with completers.

  6-week post-randomization assessments concluded on September 30, 2016 (month 28), with a total of 6 participants completing the 6-week post-randomization assessment. Participants enrolled through the open clinical trial did not complete a 6-week post-randomization assessment (see Appendix 3, IRB Amendment 2).

- **Subtask 9: Conclude Treatment and Post-Treatment Assessments.** Completed follow up phase with completers.

  Treatment and post-treatment assessments for randomized participants concluded on December 26, 2016 (month 31), with a total of 6 completing treatment and a total of 7 completing post-treatment assessments. Treatment and post-treatment assessments for open clinical trial participants concluded on 04/12/2017, with a total of 3 completing treatment and 4 completing post-treatment assessments.

- **Subtask 10: Conclude Follow Up Phase (with all completers).**
  Follow up phase concluded for randomized participants on 3/26/2017 (month 34), with 7 participants completing the 3-month follow-up. Follow-up phase is ongoing for open clinical trial participants through September 30, 2017, and 1 participant has completed the 3-month follow-up and 3 are currently scheduled.

- **Specific Aim 2, Major Task 2 – Analyze Data and Report**
  As of the end of the reporting period, subtasks 1, 3, and 4 have been completed. Subtask 2 remains ongoing.
    - **Subtask 1: Data Analysis**
    - **Subtask 2: Write up paper and results for publication**
      The results of this study are being submitted for publication in the Journal of Anxiety Disorders special issue on virtual reality therapy.
    - **Subtask #3: Submit Annual Report #2.**
      All completed with this report.
    - **Subtask #4: Submit Final Report.**
      Completed with results of the study appearing in the conclusions section.

- **What opportunities for training and professional development has the project provided?**
  - The clinical providers were trained in the operation of the software in January, 2015.
  - A Standard Operating Procedures clinical manual was created to train clinical staff in the conduct of the RCT.
  - Training and ongoing supervision in implementation of Virtual Reality Exposure Therapy.
  - Training and ongoing supervision in the conduct of clinical trials
  - Training and ongoing supervision in recruitment

- **How were the results disseminated to communities of interest?**
  - March 2017. Abstract submission to Journal of Anxiety Disorders special issue on virtual reality therapy (see Appendix 4).
  - Prior to that, presentation of the VR development occurred in >10 professional/conference talks

- **What do you plan to do during the next reporting period to accomplish the goals?**
  - Project completed. Only publication and presentation of results to follow.

4. **IMPACT**
   - **What was the impact on the development of the principal discipline(s) of the project?**
     - Although it is still in an early state of clinical efficacy testing, we have received many requests to use the system by other clinical sites. This is the first immersive VR system to be created and to be undergoing clinical tests in the area of Military Sexual Trauma and as clinical results have indicated that the system can be safely applied with positive benefits for most treatment completers, we are exploring wider dissemination of the system for further documented tests for both military and civilian treatment. The results detailed below in the Results and Conclusions section on this trial indicate that the VRET method can be safely applied and can produce positive clinical outcomes.
   - **What was the impact on other disciplines?**
     - Further support for the idea that VR is an emotionally evocative media delivery system. When used by a well-trained clinical providers to deliver an evidence-based trauma-focused treatment approach (Prolonged exposure), VR is can be safely and effectively applied. Since sexual trauma can be seen as an extreme form of trauma exposure, such

results although preliminary, bode well for other disciplines interested in using VR clinically for other emotional conditions.

- **What was the impact on technology transfer?**
    - We have interest from the commercial sector to continue this work both with Veteran and Civilian populations. The civilian oriented VR contexts match well to civilian sexual trauma and can be logically applied with that population.
- **What was the impact on society beyond science and technology?**
    - Although, the sample size is small, this study shows the first results indicating that immersive VR can be safely applied for the treatment of PTSD due to sexual trauma and that some patients significantly benefited from treatment. While this is a military Veteran sample, much of the VR content created is also applicable to civilian survivors of sexual trauma. This is particularly relevant when one notes that one in five women and one in 71 men will be raped at some point in their lives (Black et al., 2011). Prevalence of Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) PTSD associated with randomly selected sexual assaults has been reported at 20.2% (Scott et al., 2017). Moreover, the lifetime prevalence of PTSD for women who have been sexually assaulted is 50% (Creamer et al., 2001) and sexual assault is the most frequent cause of PTSD in women, with one study reporting that 94% of women experienced PTSD symptoms during the first two weeks after an assault (National Center for PTSD, 2005). The alarmingly high rate of PTSD in survivors of sexual assault is a strong indication that new therapeutic strategies are needed to address the mental health challenges faced by this population. This study is the first of its kind to take on this challenge with immersive VR-delivered treatment; it will hopefully be tested further and become a positive tool to address the emotional sequelae from this form of trauma and have a positive impact on clinical care and society. Rizzo & Koenig (2017) detail the growing impact and readiness of Clinical VR for widespread dissemination from theoretical, research, pragmatic, and ethical perspectives and from that peer-reviewed analysis, it is anticipated that this approach to PTSD treatment is expected to become widely available in the very near future.

5. **CHANGES/PROBLEMS**
    - **Changes in approach and reasons for change**
        - To increase participant recruitment, the treatment was offered through the Emory Healthcare Veterans Program 2-week Intensive Outpatient Program beginning in October 2016 (See Appendix 3, Amendment 3). Additionally, given the limited number of participants who completed the study as part of the waitlist condition (N = 1) and the limited number of participants who completed treatment before the 6-week post-randomization assessment, the six-week waitlist condition and 6-week post-randomization assessment was dropped from the treatment protocol (See Appendix 3, Amendments 1-2). Amendments were submitted to the IRB and approved on October 17, 2016. See Appendix 3 for a copy of all IRB amendments and complete rationale for the changes.

        - To address low recruitment rates, the study team increased efforts for study recruitment, including the addition of an on-hold message for Emory Healthcare offices, increased advertisements on websites and through Facebook (see Appendix 5 for further detail). Over 380,000 individuals were reached through the Facebook advertisements.
    - **Actual or anticipated problems or delays and actions or plans to resolve them**
        - A one-year no-cost extension for the project was requested and granted. The revised end date was May 26, 2017.

o As with any RCT for PTSD, recruitment challenges remained an issue. In the current year, 14 additional individuals were screened and 7 were enrolled, which was consistent with the previous year (screened 13, enrolled 8). The consistency between reporting periods further highlights that the target population for our study is one that is reluctant to report MST due to fear of reprisal, concern for military career, or shame. This challenge likely contributed to the challenges with recruitment. While the team hoped word of mouth would increase interest, the continued reluctance to disclose MST likely remained a barrier to share treatment experiences.

o The use of a waitlist condition ultimately posed a potential barrier to treatment engagement, as two of the three participants assigned to the waitlist condition did not engage in treatment. Additionally, the use of the waitlist condition as a comparison to the treatment group was not feasible due to the majority of treatment participants continuing treatment beyond the 6-week post-randomization assessment time point. In response to this problem, the study team amended the protocol, with IRB approval (see Appendix 3), to eliminate the waitlist condition and change the study to an open clinical trial.

- **Changes that had a significant impact on expenditures**
  o Nothing to report.
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
  o Nothing to report.
- **Significant changes in use or care of vertebrate animals.**
  o Not applicable
- **Significant changes in use of biohazards and/or select agents**
  o Not applicable

6. **KEY RESEARCH ACCOMPLISHMENTS**
- Virtual reality exposure therapy for PTSD due to MST was safely delivered to 13 military veterans with PTSD due to MST.
- Virtual reality exposure therapy resulted in an average reduction in clinician assessed and self-reported PTSD symptoms from pre-treatment to post-treatment assessment, with benefits persisting three months after the conclusion the study as detailed in the conclusion section below.

7. **REPORTABLE OUTCOMES**
- March 2017. Abstract submission to Journal of Anxiety Disorders special issue on virtual reality therapy (see Appendix 4).

8. **RESULTS and CONCLUSIONS from the completed trial**
Participants included 15 military veterans (seven served post 9/11) who experienced a military sexual trauma during their time in service. The majority of participants were female (N = 11). Ages ranged from 32 to 72 years (M = 46.20, SD = 10.59). Ten participants identified as black (66.7%), 4 identified as white (26.6%), and 1 identified as other (6.7%).

Participants were randomized to either the treatment condition to receive virtual reality exposure therapy immediately following the pre-treatment assessment (N = 6) or to the waitlist condition to receive virtual reality exposure therapy 6-weeks following the pre-treatment assessment (N = 3). Midway through the study, only one participant had initiated and completed treatment as part of the waitlist condition. Additionally, the majority of participants in the treatment group did not complete treatment or a majority of sessions prior to the 6-week post-randomization assessment. Therefore, participants had not reached

full benefit from treatment at that time. Given there would be insufficient data and power to make statistically and clinically meaningful comparisons between groups, the study was changed to an open clinical trial. Six additional participants were enrolled as part of the open clinical trial, resulting in a total of 15 veterans enrolled in the study. Of the total 15 participants, nine were treatment completers (i.e., completed greater than 6 sessions) and study completers (i.e., completed post and/or 3-month follow-up assessment), 2 were study completers but not treatment completers (i.e., completed fewer than 6 sessions), and four discontinued the study (2 before initiating treatment, 2 during treatment). Of note, both participants lost to the study between the pre-treatment assessment and treatment sessions were in the waitlist condition.

The study completers included 11 military veterans (five served post 9/11) who met DSM-5 criteria for PTSD, as assessed by the CAPS, and who completed the study (completed post-treatment assessment). The majority of participants were female (N = 9). Ages ranged from 37 to 54 (M = 43.73, SD = 6.65). Seven participants identified as black (63.6%), three identified as white (27.3%), and one identified as unknown or other (9.1%). There were no significant differences between study completers and study non-completers on pre-treatment measures of PTSD and depression. See Table 1 for a list of comorbid diagnoses at the pre-assessment.

<center>Results</center>

Hypothesis 1

The first hypothesis predicted that VRET would be safely deliverable to individuals with PTSD due to MST as evidenced by treatment dropout rates that are similar to existing PE delivered in military samples (20-40%) and by absence of any critical incidents. In support of the first hypothesis, no critical incidents occurred or were reported during the course of the study. Additionally, of the 15 participants enrolled in the study, 2 dropped out of the study after the pre-treatment assessment and before initiating treatment, 4 discontinued treatment early (i.e., less than 6 sessions), and 9 completed treatment, resulting in a 40% dropout rate (see Appendix 2) using the most conservative estimate. When looking at those who actually participated in the VR exposure, the dropout rate reduces to 30%, suggesting that use of VR did not lead to a comparatively inordinate dropout rate.

Hypothesis 2

The second hypothesis predicted that participants in the VRET group would show statistically and clinically meaningful reductions in PTSD and depression (PCL-5, CAPS, PHQ-9 scores and psychophysiological measures) following treatment. Paired samples t-tests, with 95% confidence intervals, were conducted to examine 1) the average change in PTSD and depressive symptoms between pre- and post-treatment assessments, and 2) the maintenance of treatment gains between post-treatment and 3-month follow-up assessments. Given only 1 person initiated and completed treatment as part of the waitlist condition, analyses were conducted for 1) study completers with pre-treatment and post-treatment assessments (N = 11), and 2) treatment completers, including those with 6 or more treatment sessions (N = 9).

In support of the second hypothesis, among study completers there was a significant reduction in pre-treatment to post-treatment clinician-assessed PTSD symptoms (CAPS severity: t(9) = 3.81, p = .004) and self-reported PTSD symptoms (PCL-5: t(9) = 3.37, p = .008); there was a marginally significant reduction in self-reported depressive symptoms, (t(7) = 2.34, p = .052). There were no significant differences between post-treatment to 3-month follow-up assessments of PTSD (CAPS severity: t(7) = 0.00, p = 1.00; PCL-5: t(7) = -1.32, p = .228) or depressive symptoms (t(5) = -0.38, p = .721), indicating a maintenance of treatment gains from post-treatment to 3-month follow-up. See Figure 1 and Table 2. Seventy-three

percent demonstrated a 30% drop in self-reported PTSD symptoms from pre-treatment to post-treatment assessments. Between those who did and those who did not demonstrate a 30% reduction, there were no significant differences in initial PTSD or depression symptoms.

Additionally, there was a significant reduction in pre-treatment to post-treatment average heart rate ($F(1,4) = 16.21$, $p = .010$) as measured during a VR simulation of common MST contexts (e.g., barracks, apartment). There was a marginally significant reduction in average EMG ($F(1,4) = 5.75$, $p = .070$), but there was no significant reduction in skin conductance ($F(1,4) = 3.70$, $p = .11$). See Figures 2-4 (below).

When examining only those who completed a full course of treatment, findings were consistent with those found among all study completers. There was a significant reduction in pre-treatment to post-treatment clinician-assessed PTSD symptoms (CAPS severity: $t(8) = 3.46$, $p = .009$) and self-reported PTSD symptoms (PCL-5: $t(8) = 3.33$, $p = .010$). There was a marginally significant reduction in self-reported depressive symptoms ($t(6) = 2.32$, $p = .059$). There were no significant differences between post-treatment to 3-month follow-up assessments of PTSD (CAPS severity: $t(6) = 0.24$, $p = .820$; PCL-5: ($t(6) = -0.82$, $p = .441$) or depressive symptoms ($t(4) = 0.40$, $p = .710$), indicating a maintenance of treatment gains from post-treatment to 3-month follow-up for treatment completers. See Figure 5 and Table 3 (below).

Figure 1. Study completers: Mean PTSD and depressive symptoms across assessment points.
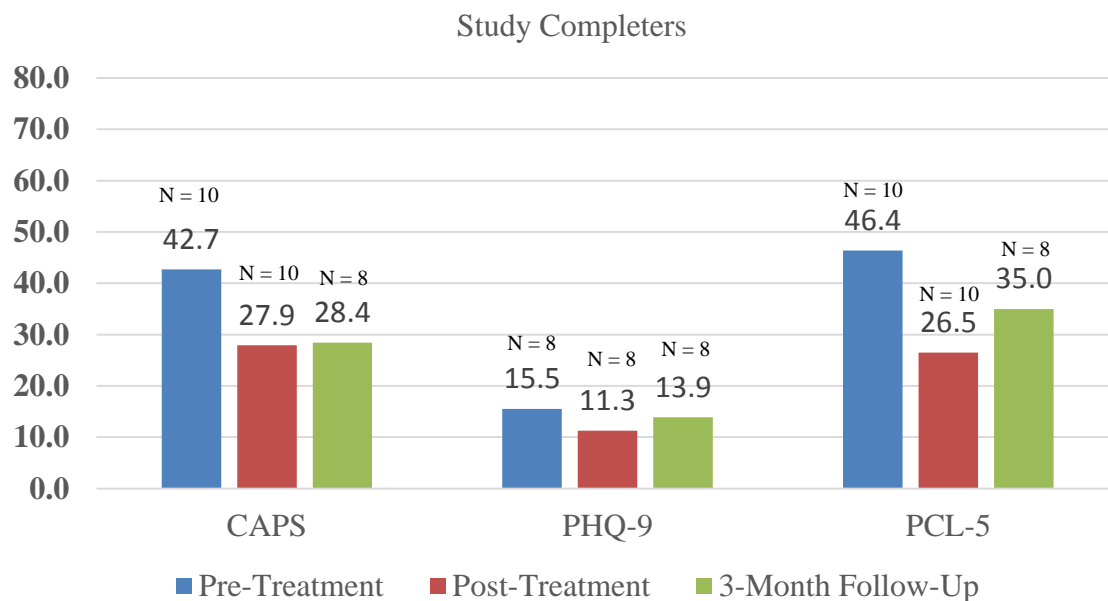
Figure 2. Change in heart rate for participants with pre-treatment and post-treatment psychophysiological data (N = 6).

Figure 3. Change in skin conductance for participants with pre-treatment and post-treatment psychophysiological data (N = 6).
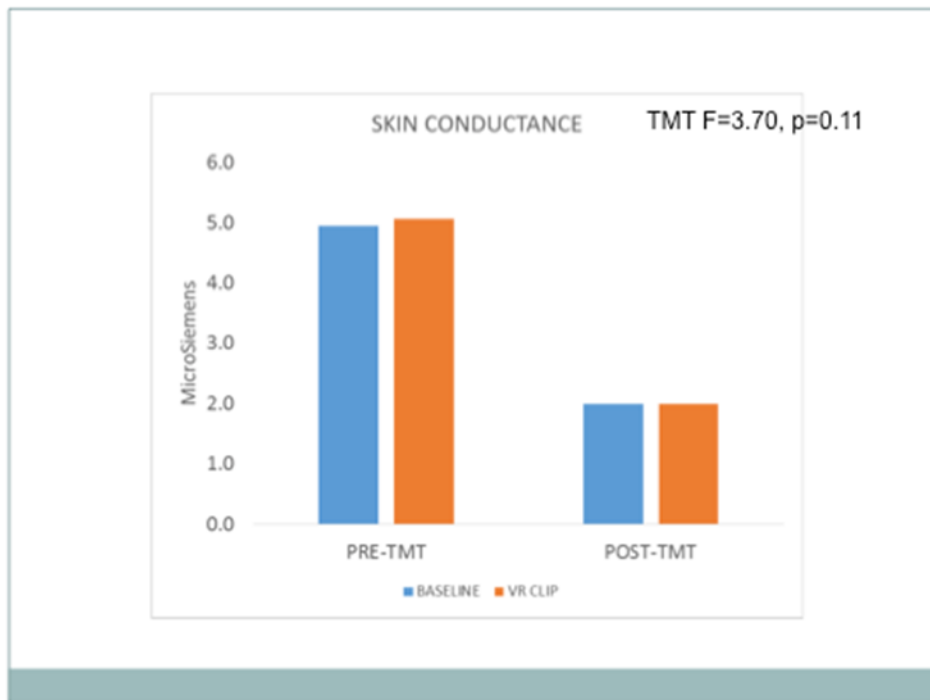
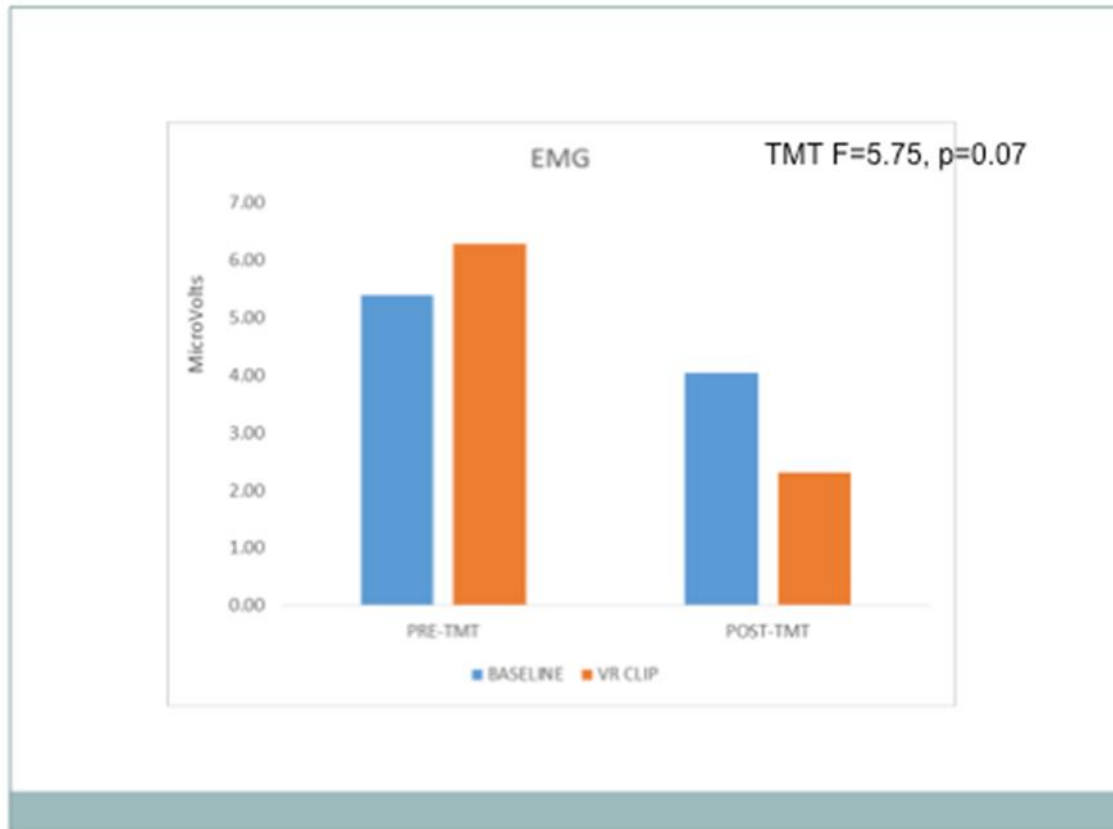*Figure 4. Change in EMG for participants with pre-treatment and post-treatment psychophysiological data (N = 6).*
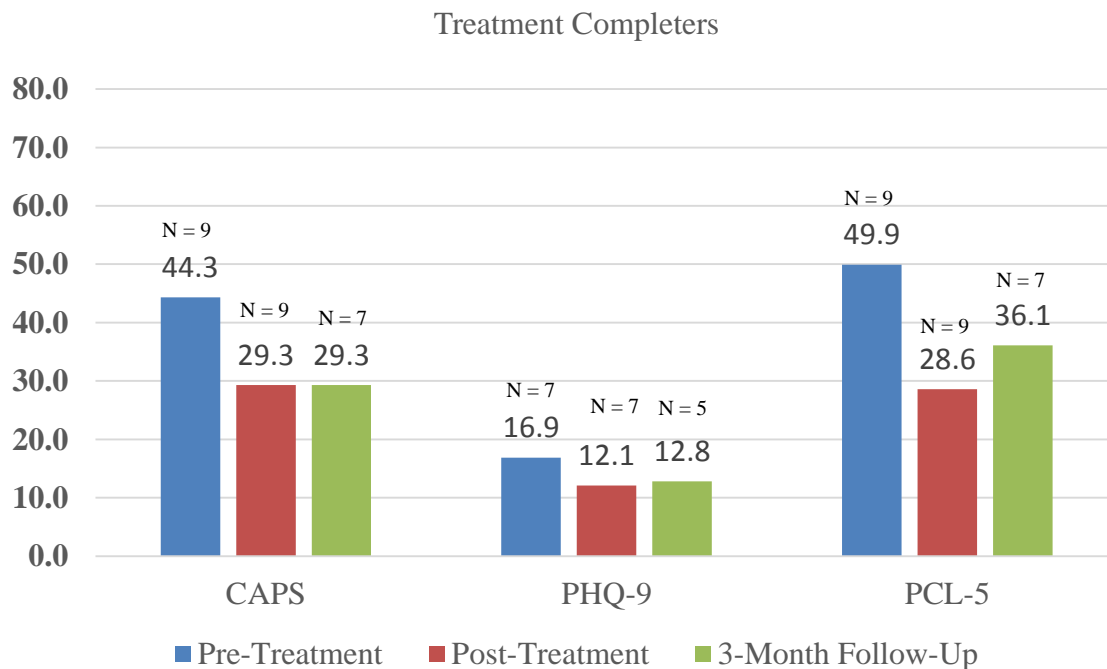

Figure 5. Treatment completers: Mean PTSD and depressive symptoms across assessment points.

Hypothesis 3

Participants in the VRET group will show statistically and clinically meaningful reductions in PTSD and depression (PCL-M, CAPS, PHQ-9 scores and psychophysiological measures) compared to waitlist results. Given the elimination of the waitlist condition, analyses were not conducted.

Exploratory Analyses

After changing the study to an open clinical trial, participants were given the option to complete the study as part of the Emory Healthcare Veterans Program 2-week Intensive Outpatient Program (Harvey, Rauch, Zalta, Sornborger, Pollack, Rothbaum, Simon, in press) (see Amendment 3). During this program, participants engaged in daily VRET therapy. There's a growing interest in intensive outpatient programs for PTSD, which may have benefits over traditional weekly session (Blount, Cigrang, Foa, Ford, & Peterson, 2014). A repeated measures ANOVA was conducted to examine whether treatment response, as assessed by the reductions in PTSD and depressive symptoms, was greater for participants who enrolled in the 2-week program versus traditional weekly sessions. There was a significant main-effect of time (pre-treatment to post-treatment assessment) on self-reported and clinician-assessed PTSD symptoms (CAPS: $F(1,9) = 10.72$, $p = .010$; PCL-5: $F(1,9) = 9.00$, $p = < .001$) and self-reported depressive symptoms (PHQ-9: $F(1,9) = 13.76$, $p = .008$), such that symptoms declined from pre-treatment to post-treatment assessments. There was a significant interaction between time and IOP participation for self-reported PTSD symptoms ($F(1, 9) = 7.92$, $p = .024$), such that there was a significant reduction in PTSD symptoms from the pre-treatment to post-treatment assessment, and this was particularly true for those participants who completed treatment as part of the 2-week intensive outpatient program (pre: M = 54.25, SD = 17.22; post: M = 19.00, SD = 8.29) versus traditional weekly outpatient program (pre: M = 43.0, SD = 17.22; post: M = 31.29, SD = 23.60). There were no significant interactions between time and clinician-assessed PTSD symptoms or self-reported depressive symptoms.

Case Vignettes

Given the small sample size and the complexity in trauma experiences, psychosocial stressors, and varied mental health diagnoses among the MST participants, individual case vignettes are presented for all participants who enrolled in the study (N = 15). Each vignette provides a brief overview of demographics, participation in the study, and outcomes as available (see Appendix 6, Case Vignettes).

<u>Conclusion</u>

The goal of the current pilot study was to examine the safety, feasibility and efficacy of implementing virtual reality exposure therapy (VRET) for the treatment of PTSD due to MST. Results from the study are promising. In support of the first hypothesis, the most conservative estimate of the dropout rate in the current study was 40% (30% for those who experienced VR exposure), which was consistent with other prolonged exposure therapy dropout rates in military samples. Additionally, there were no adverse effects or critical incidents in response to VRET implementation. Thus, BM virtual reality exposure therapy has demonstrated safety and feasibility for implementation in MST treatment. In support of the second hypothesis, study completers evidenced significant reductions in clinician-assessed and self-reported PTSD symptoms from pre-treatment to post-treatment assessments, and these gains were maintained at the 3-month follow-up. There also was a significant reduction in heart rate, as assessed during exposure to virtual reality MST contexts (e.g., hotel room, barracks) at pre-treatment and post-treatment assessments; however, there were no significant reductions in skin conductance or EMG, although trends in this direction were observed. Therefore, in this sample virtual reality reduced self-assessed, clinician assessed, and some physiological indicators of PTSD. In addition to PTSD symptoms, depressive symptoms also declined from the pre-treatment to post-treatment assessment; however, the reductions were only

marginally significant. These gains also were maintained at the 3-month follow-up. Findings indicate that VRET effectively reduced and treated PTSD.

While VRET resulted in a decline in depressive symptoms, the reduction was only marginal in significance. As demonstrated in the case vignettes, the sample of veterans with MST who completed the study had numerous and significant life stressors before, during, and after treatment. Self-report assessments are sensitive to these general daily stressors and likely reflect distress that persisted beyond the PTSD treatment of military sexual trauma. Additionally, among veterans presenting to a VA PTSD clinic, those endorsing primary MST-related versus combat-related trauma were more likely to experience greater depressive symptoms; however, there were differences in PTSD symptomatology between those with combat versus military sexual trauma (Sexton, Raggio, McSweeney, Authier, & Rauch, 2017). Therefore, additional treatment in support of life stressors might further alleviate distress after PTSD has been addressed.

A final goal of the study was to demonstrate that participants in the VRET group would show statistically and clinically meaningful reductions in PTSD and depression (PCL-M, CAPS, PHQ-9 scores and psychophysiological measures) compared to waitlist results. The final goal was not met due to unforeseen challenges in the current study, leading to the elimination of the waitlist condition. Only one of three waitlist condition participants engaged in treatment, and the majority of treatment condition participants did not reach a full dose of treatment by the 6-week post-randomization assessment.

Exploratory analyses examined whether participants engaging in VRET as part of a 2-week intensive outpatient program (daily sessions) would have greater reductions in PTSD and depressive symptoms than those engaging in weekly outpatient program (one to two sessions per week). Participants who engaged in VRET as part of the IOP had significantly greater reductions in self-reported PTSD symptoms from pre-treatment to post-treatment assessments than those engaging in weekly treatment. However, all participants demonstrated significant reductions in PTSD and depressive symptoms, regardless of IOP or OP involvement. While all participants' symptoms improved over time, it's possible that the intensive dose can further enhance participants' response to VRET for MST. Additionally, all IOP participants completed the study. Findings suggest that the IOP might be a beneficial format for treating veterans with PTSD due to MST, and indicate that VRET is tolerated in this format. This is the first known study that has examined VRET in MST in this intensive treatment format.

A primary limitation to the current pilot study was the small sample size, which likely attenuated study findings and outcomes. With a goal of enrolling 20 participants (36 initially) to be randomized into treatment and waitlist condition groups, the study did not meet this benchmark. By the end of the first year of recruitment, only eight participants were enrolled in the study, and an additional 7 participants enrolled in the study during the second year. Given that the overall study dropout rates were consistent with dropout rates for prolonged exposure therapy, the challenges in the current study were primarily due to low recruitment. Of the 27 participants who called with interest in the study, five were scheduled for a pre-assessment but did not show. A potential explanation is the role of avoidance. With avoidance as a hallmark symptom of PTSD, engagement in PTSD therapy is a challenge for all individuals, and likely more challenging for veterans with PTSD due to MST. The case vignettes illustrate the complexity of the MST population, with numerous social stressors and diagnoses in addition to PTSD. Additionally, the waitlist condition likely posed an additional, unexpected barrier for engagement, with two of the three waitlist participants dropping from the study before treatment. The potential of a waitlist might have further hindered enrollment in the study, particularly if participants already were avoidant of confronting trauma memories. Future studies will benefit from examining the use of VRET in treating PTSD with a larger sample.

Overall, the pilot study demonstrated that VRET is likely a safe and effective treatment for PTSD due to MST. Despite the complexity of the MST population, participants, on average, experienced reductions in PTSD symptoms that were maintained 3-months following treatment. Additionally, VRET can be effectively and safely implemented in an intensive treatment format, which seems to increase treatment benefit.

9. **PRODUCTS**
   - **Publications, conference papers, and presentations**
     - **Journal publications**
       - Norrholm, S.D., Jovanovic, T., Gerardi, M., Breazeale, K.G., Davis, M., Duncan, E.J., Ressler, K.J., Bradley, B., Rizzo, A.A., & Rothbaum, B.O. (2016). Psychophysiological and Cortisol Reactivity as a Predictor of PTSD Treatment Outcome in Virtual Reality Exposure Therapy. Behaviour Research and Therapy, 82: 28-37.
       - Rizzo, A. A. & Shilling, R. (in press). Clinical Virtual Reality Tools to Advance the Prevention, Assessment, and Treatment of PTSD. European Journal of Psychotraumatology.
       - Rizzo, A.A., Cukor, J., Gerardi, M., Alley, S., Reist, C., Roy, M., Rothbaum, B.O., & Difede, J. (2015). Virtual Reality Exposure Therapy for PTSD due to Military Combat and Terrorist Attacks. Journal of Contemporary Psychotherapy. 45: Early Online. DOI 10.1007/s10879-015-9306-3
       - Rizzo, A.A., Hartholt, A., Grimani, M., Leeds, A. & Liewer, M. (2014). Virtual Reality Exposure Therapy for Treating Combat-Related PTSD. IEEE Computer. July, 2014. 31-37.
     - **Books or other non-periodical, one-time publications**
       - Safir, M., Wallach, H. & Rizzo, A.A. (2014). Future Directions in Post-Traumatic Stress Disorder: Prevention, Diagnosis, and Treatment. Springer, Inc., NY, NY.
     - **Other publications, conference papers, and presentations**
       - Rizzo, A.A., Roy, M., Hartholt, A., Costanzo, M., Highland, K.B., Jovanovic, T., Norrholm, S.D., Reist, C., Rothbaum, B.O., & Difede, J. (2017). Virtual Reality Applications for the Assessment and Treatment of PTSD. In Bowles, S. & Bartone, P.T. (eds.): Military Psychology: Clinical and Organizational Practice. Springer, Inc., NY, NY.
       - Roy, M.J., Rizzo, A.A., Difede, J. & Rothbaum, B.O. (2017). Virtual Reality Exposure Therapy. In: D. Benedek, and G. H. Wynn (Eds), Complimentary and Alternative Approaches to the management of PTSD. Oxford University Press.
       - Rizzo, A.A. (2017). Clinical Virtual Reality: Applications for Anxiety Disorders, PTSD, and Pain Management. University of Otago Psychology Dept. Colloquium, Dunedin, New Zealand, April 10, 2017.
       - Rizzo, A.A. (2016). Clinical Virtual Reality: Exposure Therapy for the Prevention, Assessment and Treatment of PTSD and Beyond. VR Summit. San Diego, CA., Dec. 15, 2016.
       - Rizzo, A.A. (2016). Virtual Reality Systems for the Prevention, Assessment, & Treatment of PTSD. Invited Master Methodologist Keynote at the 32nd Annual Meeting of the International Society for Traumatic Stress Studies. Dallas, TX. November 11, 2016.
       - Rizzo, A.A. (2016). Clinical Virtual Reality: A Brief Review of VR Applications for Trauma and other Clinical Conditions. Presentation at the 32nd Annual Meeting of the International Society for Traumatic Stress Studies. Dallas, TX. November 10, 2016.

- Rizzo, A.A. (2016). Clinical Virtual Reality: Exposure Therapy for the Prevention, Assessment and Treatment of PTSD and Beyond. CSULB Psychology Department colloquium. Long Beach, CA., Oct. 26, 2016.
- Rizzo, A.A. (2016). Reducing the Psychological Pain of PTSD with Virtual Reality Exposure Therapy. VRPain 2016. Los Angeles, CA., September 19, 2016.
- Rizzo, A.A. (2016). Virtual Reality Exposure Therapy for PTSD and Beyond. The 2nd Virtual Reality and Hidden Wounds of War Conference. Los Angeles, CA., September 20, 2016.
- Rizzo, A.A. (2016). Virtual Reality Goes to War: Advances in the Prevention of Posttraumatic Stress. Invited Keynote at NATO Summit on Resilience and PTSD. Bucharest, Romania. April 12, 2016.
- Rizzo, A.A. (2016). Clinical Virtual Reality Applications to Address the Wounds of War. Workshop presented at the Tampa VA. Tampa Fl. Jan. 19, 2016.
- Rizzo, A.A. (2015). Virtual Reality Goes to War: Advances in the Prevention, Assessment, and Treatment of Posttraumatic Stress. Invited presentation at ETH Zurich, Swiss Federal Institute for Technology. Dec. 8, 2015.
- Rizzo, A.A. (2015). Virtual Reality Goes to War: Advances in the Prevention of Posttraumatic Stress. Invited Keynote at TNO: Netherlands Organisation for Applied Scientific Research. Eindhoven, Netherlands. November 3, 2015.
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- Rizzo, A.A. (2016). Clinical VR: A Visit to the Future of Therapy Practice. Psychotherapy Networker Conference. Wash.D.C. March 18, 2016.
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- Rizzo, A.A. (2015). Virtual Reality Goes to War: Advances in the Prevention of Posttraumatic Stress. Invited Keynote at TNO: Netherlands Organisation for Applied Scientific Research. Eindhoven, Netherlands. November 3, 2015.
- Rizzo, A.A. (2015). Virtual Reality Goes to War and Beyond. Invited presentation at the Sydney Disrupt conference, Sydney Australia. September 24, 2015.
- Rizzo, A.A. (2015). Virtual Reality Goes to War. Invited presentation to MITRE/Red Sox, My Homebase Vets Support Program. Boston, MA. Sept. 8, 2015.

- Rizzo, A.A. (2015). Clinical Virtual Reality: A Brief Review of the Future. LA StoryCode Event. August 19, 2015.
- Rizzo, A.A. (2015). Virtual Reality Goes to War: Application for the Prevention, Assessment, and Treatment of PTSD. Invited presentation at Stanford University. July 13, 2015.
- Rizzo, A.A. (2015). Virtual Reality Goes to War: Innovations in Veteran Behavioral Healthcare. Invited presentation at the Los Angeles VA Medical Center. March 23, 2015.
- Rizzo, A.A. (2015). Clinical Virtual Reality: Application to Address the Wounds of War. Invited Colloquim Talk at the Binghamton University Psychology Dept. Binghamton, NY, March 16, 2015.
- Rizzo, A.A. (2015). Using Virtual Reality Simulation Technology to Support Military Mental Health and Resilience. West Point Human Performance Optimization Workshop. West Point, NY. Feb. 26, 2015.
- Rizzo, A.A. (2014). Virtual Reality goes to War: New Tools for preventing, assessing and treating PTSD. Invited presentation at the Naval Health Research Center – San Diego, CA. December 4, 2014.
- Rizzo, A.A. (2014). Virtual Reality goes to War: Simulation Tools for preventing, assessing and treating PTSD. Invited Talk at West Point, West Point, NY, November 21, 2014.
- Rizzo, A.A. (2014). Virtual Reality goes to War: The Future use of VR to Prevent and Treat PTS. Invited address to the Summa Healthcare Network. Akron, Ohio, November 13, 2014.
- Rizzo, A.A. (2014). Virtual Reality goes to War: Advances in the Assessment and Treatment of Posttraumatic Stress. Invited opening talk at the Web Summit. Dublin Ireland. November 4, 2014.
- Rizzo, A.A. (2014). Virtual Reality and Treatment of Posttraumatic Stress. Invited speaker at L.A. Library's Odyssey Project: The Warriors Return: From Surge to Suburbia With David Finkel and Skip Rizzo. Los Angeles, CA. October 27, 2014.
- Rizzo, A.A. (2014). Virtual Reality goes to War: Advances in the Assessment and Treatment of Posttraumatic Stress. The 2nd Annual Infinite Hero's Foundation Veterans Summit. Irvine, CA., September 15-16, 2014.
- Rizzo, A.A. (2014). Update and Expansion of the Virtual Iraq/Afghanistan PTSD Exposure Therapy System. The 122nd Annual Convention of the American Psychological Association. Washington D.C. August 7, 2011.

- **Website(s) or other Internet site(s)**
  - The ICT Website provides information on the overall research program. http://ict.usc.edu/
  - The ICT MedVR Youtube Channel has over 40 videos on the various elements of the BRAVEMIND project: http://www.youtube.com/user/albertskiprizzo
  - http://psychiatry.emory.edu/research/clinical_trials/ptsd/rothbaum_MilitarySexTrauma.html
- **Technologies or techniques**
  - This is the first immersive VR system to be created and undergo clinical tests in the area of Military Sexual Trauma. We have received commercial interest in expanding BRAVEMIND dissemination for both military and civilian treatment. Based on the safety and efficacy results of this project the MST content will be bundled with the standard BRAVEMIND software package to support future efforts to expand the research started here and document its safe use and value. Both previous iterations of our PTSD VR exposure therapy software has been deployed to over 100 sites. The current BRAVEMIND system is located at approximately 50 sites.
- **Inventions, patent applications, and/or licenses**

- o None.
- **Other Product**
  - o None
- **Identify any other reportable outcomes that were developed under this project.**
  - o None.

10. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:
- **What individuals have worked on the project?**

Name:	Dr. Albert Rizzo
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	skiprizzo (eRA Common)
Nearest person month worked:	1
Contribution to Project:	Dr. Rizzo has led the project and provided scenario and study design from a clinical psychology perspective.
Funding Support:	N/A

Name:	David Kwok
Project Role:	Special Project Manager
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Mr. Kwok oversaw project operations, maintained the budget and the milestone schedule, and assisted with purchasing of equipment, travel, and supplies. He also supported the project team and consultants.
Funding Support:	N/A

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - o Nothing to Report.
- **What other organizations were involved as partners?**
  - o **Organization Name:** Emory University
  - o **Location of Organization:** Atlanta, GA
  - o **Partner's contribution to the project**: IRB approval process, hire and train study personnel, recruit subjects, assess participants, treat participants, provide follow-up assessments, assist with data analysis, and assist with write-up of paper and results for publication.
  - o **Financial support:** Subcontract
  - o **In-kind support:** None
  - o **Facilities:** RCT will take place at Emory University.

- o **Collaboration:** Emory University provided subject matter expertise in scenario design and is running the RCT.
- o **Personnel exchanges:** None

11. FIGURES
Figure 1. Bravemind Military Sexual Trauma PTSD Virtual Reality Exposure Therapy System Images

US Base and Town Outdoor Content:

US Base and Town Indoor Spaces:

Forward Operating Base Content:

Figure 2. Forward Operating Base Scenario Clinician Interface.

Figure 3. US Base and Town Scenario Clinician Interface.

Created by the USC Institute for Creative Technologies. PI: Skip Rizzo

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13. APPENDICES

APPENDIX 1: Patient Assessment

Pre-Treatment Assessment

Potential subjects will be asked to provide a copy of their DD214 to verify their military service record. Once a potential participant has met all screening inclusion and exclusion criteria and consented to participate, the CAPS will be administered to determine current PTSD status.

The Clinician Administered PTSD Scale (CAPS; Blake et al., 1990, 1995; updated for DSM V). This is an interviewer-administered diagnostic instrument that measures PTSD. The CAPS provides a diagnostic measure of PTSD and a continuous measure of the severity, frequency, and intensity of the three symptom clusters (intrusion, avoidance, and arousal) and overall PTSD. If positive for current PTSD on the CAPS, and all other eligibility criteria are fulfilled, the rest of the pre-treatment measures will be administered.

The Demographics Questionnaire. This covers demographics, family composition, personal psychiatric history, and income and education information to obtain a Hollingshead Four Factor Scale of Socioeconomic Status.

The Childhood Trauma Questionnaire (CTQ; Bernstein, et al., 2003). This is a self-report measure which assesses history of childhood trauma employing a Likert-scale format with 5 responses per item.

The Emory Treatment Resistance Interview for PTSD (E-TRIP). This is a structured interview that assesses prior trials of pharmacology and psychotherapy PTSD treatments and provides a quantitative indicator of PTSD treatment resistance.

PTSD Checklist for DSM-5 (PCL-5). The PCL-5 is a 20-item self-report measure that assesses the 20 DSM 5 symptoms of PTSD. The PCL-5 has been shown to be equivalent to the well-validated PCL-S.

The MINI International Neuropsychiatric Interview (M.I.N.I.; Sheehan, D. V. et al., 1998). This will be administered to screen axis 1 disorders and to establish co-morbid diagnosis.

The Beck Depression Inventory-II (BDI; Beck, Steer, & Brown, 1996). This is a 21-item measure of cognitive and vegetative symptoms of depression is widely used in a variety of populations, including trauma victims and is sensitive to treatment effects on depression.

State Trait Anxiety Inventory (STAI; Spielberger et al., 1970). The STAI-State is a 20-item self-report scale employing a Likert scale format with 4 responses per item (1-4). Ten of the STAI items measure feelings of stress and anxiety, while the remaining ten items measure feelings of relaxation.

Deployment Risk and Resiliency Inventory (DRRI; King, King, & Vogt, 2003). This is a self-report measure of pre-deployment, deployment and post-deployment experiences and trauma specific to the veteran population. The scale employs yes-no and Likert scale format responses ranging from 1-5.

The Quality of Life Inventory (QOLI; Frisch et al., 1992). The QOLI consists of 16 items selected to include all areas of life that have been empirically associated with life satisfaction. Respondents rate how important each of the 16 domains is to their overall satisfaction and happiness; they then rate how satisfied they are in the area. The total score reflects one's satisfaction in areas that one considers

important to them. The QOLI's sensitivity to treatment-related change has been demonstrated with clinical samples of depressed, socially anxious/phobic, and chemically-dependent patients.

Clinical Global Impressions Scale, Severity of Illness (CGI-Severity; Guy & Bonato, 1970). This is a study personnel rated measure of severity of illness ranging from 0 (not assessed) to 7 (among the most extremely ill patients).

The Columbia–Suicide Severity Rating Scale. (Columbia; Posner et al., 2011). The Columbia–Suicide Severity Rating Scale was initially designed to assess suicidal ideation and behavior in clinical trials. It assesses occurrences, types, and severity of suicidal ideation and all types of behavior.

Neurobehavioral Symptom Inventory (NSI; Mererko et al., 2012). This is a 22-item measure designed to assess postconcussive symptoms following deployment-related mild traumatic brain injury among veterans.

Patient-Reported Outcomes Measurement Information System 8a and 4a -Satisfaction with Social Roles and Activities (PROMIS 4a, PROMIS8a, (Cella et al., 2010). The PROMIS item bank assesses satisfaction with performing one's usual social roles and activities.

The Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams 2001). The PHQ-9 is assesses each of the 9 DSM-IV criteria for depression as "0" (not at all) to "3" (nearly every day).

The Alcohol Use Disorders Identification Test—Consumption (AUDIT-C; Frank, Danielle et al. 2008). The AUDIT-C is a brief validated self-report screen for risky drinking and alcohol abuse and dependence (alcohol misuse). It has three questions that ask the frequency and amount of alcohol consumed.

Psychophysiological Patient Report. This is a brief self-report administered following each psychophysiological assessment. Using a Likert scale (Not at all to Very/Severe) participants rate the assessment VE as to 1. How closely the video matched their experience and 2. How distressing they found the video.

Intent to Attend (Leon et al., 2007). This is a short, two question survey asking participants how likely they are to complete all of the study and how likely they are to attend the next session.

Oragene DNA Collection (optional). If the participant agrees, they will provide a 2mL sample of saliva for DNA analysis.

Psychophysiological Reactivity Assessment. Acoustic startle response, skin conductance, and heart rate will be assessed during a viewing of three VR scenes. The VR scenes will be presented through a head-mount display for 15 minutes. Psychophysiological data collection is described below.

SimSensei Rating Scale. This is a brief questionnaire assessing how comfortable and engaged the patient feels about interacting with a virtual human in the SimSensei video.

Measures at Therapy Session

Expectancy of Therapeutic Outcome Questionnaire (ETOQ). This assesses how logical the treatment appears and the expectancy of success for the patient and for others. This measure is administered after session 1 only.

Standardized Trauma Interview (STI; Foa & Rothbaum 1998). The STI was modified for this study and will be used to gather information on relevant aspects of the trauma and demographic information to be used in exploratory analyses to predict response to treatment. This measure is administered during session 1 only.

Clinical Global Impressions Scale, Severity of Illness (CGI-Severity; Guy & Bonato, 1970). This is a study personnel rated measure of severity of illness ranging from 0 (not assessed) to 7 (among the most extremely ill patients). This measure is administered after sessions 1–12.

Clinical Global Impression – Improvement (CGI-Improvement; Guy & Bonato, 1970). This is a study personnel rated measure of patient's improvement since start of study ranging from 1 (very much improved) to 7 (very much worse). This measure is administered after sessions 2-12.

Clinical Global Improvement Scale, Patient Report (CGI - Self Report; Guy & Bonato, 1970). This is a self-reported global measure of change in severity of symptoms, ranging from 1 (*very much improved*) to 4 (*unchanged*) to 7 (*very much worse*). This measure is administered after sessions 1-12.

PTSD Checklist for DSM-5 (PCL-5). The PCL-5 is a 20-item self-report measure that assesses the 20 DSM 5 symptoms of PTSD. The PCL-5 has been shown to be equivalent to the well-validated PCL-S.

Subjective Units of Discomfort (SUDs). This will be gathered during each exposure session. Participants will be asked to rate their level of discomfort on a scale of 0 (no anxiety) to 100 (panic levels of anxiety) every 5 minutes during the VR exposure.

Intent to Attend (Leon et al., 2007). This is a short, two question survey asking participants how likely they are to complete all of the study and how likely they are to attend the next session.

Measures at each onsite assessment visit following Pre-Assessment: Non EHVP IOP (all assessments), EHVP IOP (post treatment assessment, and, if completed onsite, the 3-month follow-up)
- The Clinician Administered PTSD Scale (CAPS) see above
- The Beck Depression Inventory (BDI) as above.
- The PTSD Checklist-Military (PCL-5) as above.
- The Clinical Global Improvement Scale (Severity, Improvement, and Patient Report) as described above.
- The Quality of Life Inventory as above.
- The State Trait Inventory as above.
- Neurobehavioral Symptom Inventory (NSI) as above.
- Patient-Reported Outcomes Measurement Information System 8a and 4a -Satisfaction with Social Roles and Activities (PROMIS 4a, PROMIS8a) as above.
- The Patient Health Questionnaire (PHQ-9) as above
- The Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) as above
- Patient Update Interview: This a brief interview administered to obtain general patient follow-up data, i.e. between-assessment treatment, medication changes, substance use status/changes, and patient report on relationship/employment/health changes.
- Psychophysiological Patient Report as above.
- SimSensei Rating Scale (as above).

Measures at each remote assessment visit: EHVP IOP Participants (3-month follow-up)
- The Clinician Administered PTSD Scale (CAPS) see above
- The Beck Depression Inventory (BDI) as above.
- The PTSD Checklist-Military (PCL-5) as above.

- The Clinical Global Improvement Scale (Severity, Improvement, and Patient Report) as described above.
- The Quality of Life Inventory as above.
- The State Trait Inventory as above.
- Neurobehavioral Symptom Inventory (NSI) as above.
- Patient-Reported Outcomes Measurement Information System 8a and 4a -Satisfaction with Social Roles and Activities (PROMIS 4a, PROMIS8a) as above.
- The Patient Health Questionnaire (PHQ-9) as above
- The Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) as above
- Patient Update Interview: This a brief interview administered to obtain general patient follow-up data, i.e. between-assessment treatment, medication changes, substance use status/changes, and
- Patient report on relationship/employment/health changes.

Psychophysiological Assessment:

Pre-treatment, 6 weeks post-randomization, and 3 month follow up. Psychophysiological data will be acquired at a sampling rate of 1kHz, amplified and digitized using the EMG module of the Biopac MP150 for Windows (Biopac Systems, Inc., Aero Camino, CA).

- The acoustic startle response (eye blink component) will be measured via electromyographic (EMG) recordings of the right *orbicularis oculi* muscle. Two 5 mm Ag/AgCl pre-gelled disposable electrodes will be positioned approximately 1 cm under the pupil and 1 cm below the lateral canthus. The startle probe (noise burst) will be a 108-dB (A) SPL, 40-ms burst of broadband noise with a near instantaneous rise time.
- Skin conductance level and skin conductance response will be acquired at a sampling rate of 1 kHz using the GSR module of the Biopac system. Two 5 mm Ag/AgCl disposable electrodes filled with isotonic paste will be attached to middle phalanges of the second and fourth finger of the non-dominant hand.
- Heart-rate and heart-rate variability (HRV) will be measured using the ECG module of the Biopac system at a sampling rate of 1 kHz. One 5mm Ag/AgCl electrode will be placed on the chest above the right clavicle; another electrode will be placed on the chest under the left side of the ribcage.
- Four saliva samples will be obtained from participants for measuring cortisol.

SimSensei sessions:

Participants will be interviewed by a virtual human for approximately 15 minutes. Psychophysiological measures will be collected during the presentation of the SimSensei using Biopac MP150 System EMG, GSR and ECG modules as described above. These measures are non-invasive and will provide minimal interference with the SimSensei presentation, yet will provide objective measures of both arousal and valence. EMG of the corrugator muscle will provide an index of negative facial expressions, while skin conductance will measure arousal and sympathetic nervous system activity. The ECG data will provide measures of heart rate (HR) and heart rate variability (HRV) as an index of vagal control of cardiovascular function. All of these measures are associated with emotion regulation and have been associated with PTSD symptoms.

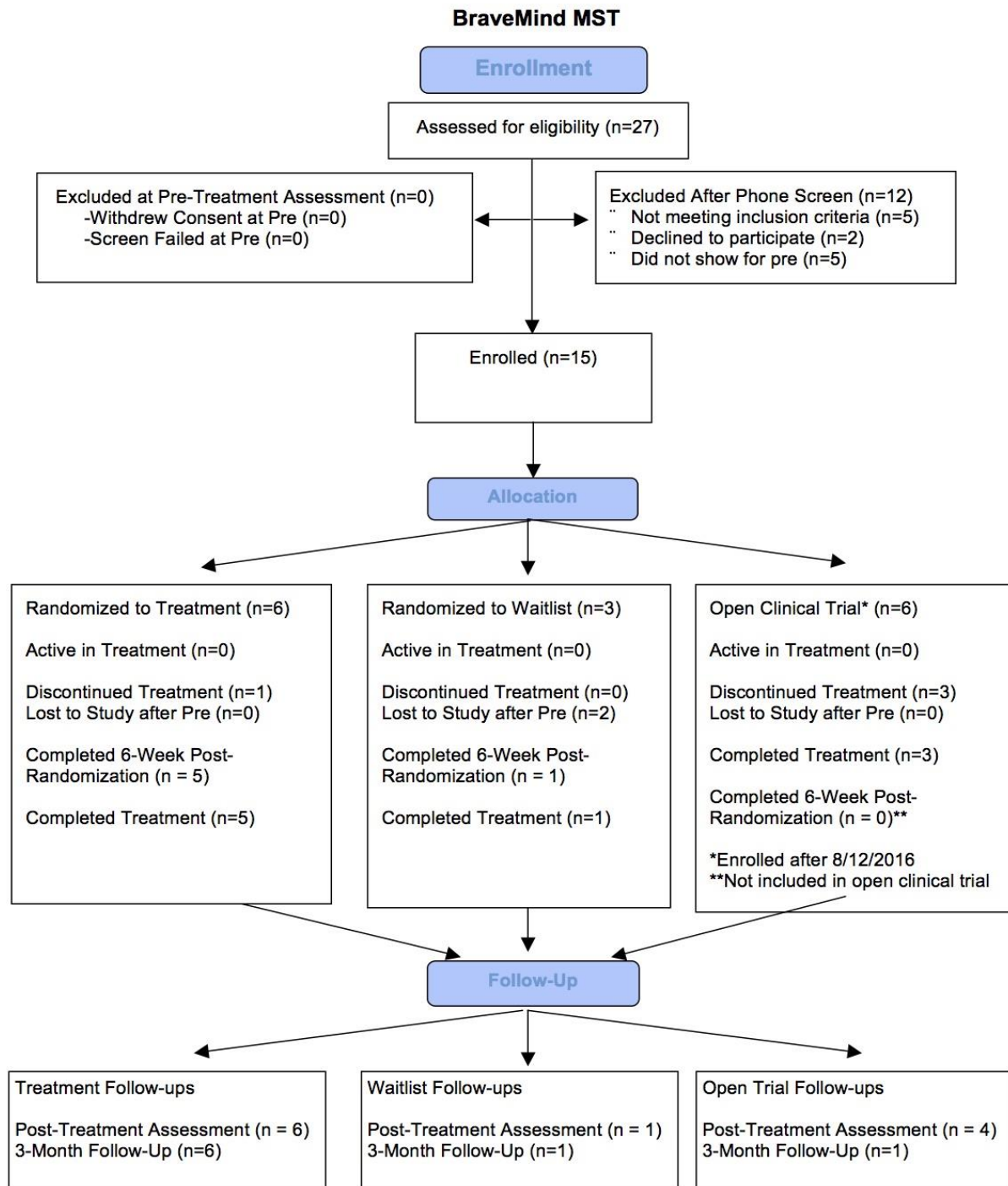Study Timepoint (Non EHVP IOP Participants and All onsite IOP Assessments)

	Pre	Therapy	Post Treatment	3 Month Follow Up
CAPS	x		x	x
STI		x		
Demographics Update	x			
Interview			x	x
CTQ	x			
E-TRIP	x			
PCL-5	x	x	x	x
MINI	x			
BDI	x		x	x
STAI	x		x	x
DRRI	x			
QOLI	x		x	x
ITA	x	x	x	
Columbia	x			
NSI	x		x	x
PROMIS	x		x	x
PHQ-9	x		x	x
Audit-C	x		x	x
DNA	x			
ETOQ	x			
CGI-Severity	x	x	x	x
CGI-Clinician		x	x	x
CGI- Patient		x	x	x
SUDS		x		
Psychophys	x		x	x
Psychophys- SR	x		x	x
SimSensei	x		x	x
SimSensei SR	x		x	x

Study Timepoint (EHVP IOP Participants w/Remote 3-Month Follow-up)

	Pre	Therapy	Post Treatment	3 Month Follow Up
CAPS	x		x	x
STI		x		
Update Interview			x	x
Demographics	x			
CTQ	x			
E-TRIP	x			
PCL-5	x	x	x	x
MINI	x			
BDI	x		x	x
STAI	x		x	x
DRRI	x			
QOLI	x		x	x
ITA	x	x	x	
Columbia	x			
NBI	x			
PROMIS	x			
PHQ-9	x			
Audit-C	x			
DNA	x			
ETOQ	x			
CGI-Severity	x	x	x	x
CGI-Clinician		x	x	x
CGI- Patient		x	x	x
SUDS		x		
Psychophys	x			x
Psychophys- SR	x			x
SimSensei	x			x
SimSensei SR	x			x

APPENDIX 2: Consort Table

BraveMind MST

Enrollment

Assessed for eligibility (n=27)

Excluded at Pre-Treatment Assessment (n=0)
  -Withdrew Consent at Pre (n=0)
  -Screen Failed at Pre (n=0)

Excluded After Phone Screen (n=12)
  ¨ Not meeting inclusion criteria (n=5)
  ¨ Declined to participate (n=2)
  ¨ Did not show for pre (n=5)

Enrolled (n=15)

Allocation

Randomized to Treatment (n=6)

Active in Treatment (n=0)

Discontinued Treatment (n=1)
Lost to Study after Pre (n=0)

Completed 6-Week Post-Randomization (n = 5)

Completed Treatment (n=5)

Randomized to Waitlist (n=3)

Active in Treatment (n=0)

Discontinued Treatment (n=0)
Lost to Study after Pre (n=2)

Completed 6-Week Post-Randomization (n = 1)

Completed Treatment (n=1)

Open Clinical Trial* (n=6)

Active in Treatment (n=0)

Discontinued Treatment (n=3)
Lost to Study after Pre (n=0)

Completed Treatment (n=3)

Completed 6-Week Post-Randomization (n = 0)**

*Enrolled after 8/12/2016
**Not included in open clinical trial

Follow-Up

Treatment Follow-ups

Post-Treatment Assessment (n = 6)
3-Month Follow-Up (n=6)

Waitlist Follow-ups

Post-Treatment Assessment (n = 1)
3-Month Follow-Up (n=1)

Open Trial Follow-ups

Post-Treatment Assessment (n = 4)
3-Month Follow-Up (n=1)

APPENDIX 3: IRB Amendments to change randomized clinical trial to open clinical trial.

IRB approval for changes granted 10/17/2016.

Amendment 1: Change study to an open clinical trial rather than randomized clinical trial by dropping the waitlist condition and enrolling all participants immediately into treatment.

Amendment 1 Rationale: Of the 9 randomized participants, only 3 have been assigned to waitlist, and 2/3 were lost prior to initiating treatment. Additionally, the majority of our Treatment Condition participants do not complete 6 therapy sessions (full treatment dose) by the 6 week post randomization assessment point. Therefore, using this assessment point as a comparison between groups will not reflect treatment gains sufficient for comparing treatment and waitlist conditions. In an effort to treat the greatest number of participants we would like to eliminate the waitlist condition and enroll all participants immediately into treatment.

Amendment 2: Eliminate 6-week post randomization assessment for all future participants. Add psychophysiological assessment and Simsensei to post-treatment assessment. Assessment format will be identical to the current 6 week post randomization and 3-month follow-up assessment points. Compensation for post-treatment assessment will be increased from $20 to $50 to reflect the increase in time spent completing the assessment.

Amendment 2 Rationale: Consistent with the rationale for Amendment 1 and given the elimination of randomization, the 6-week post randomization assessment point is no longer warranted for analysis of study outcomes. Additionally, maintaining this assessment point would be an unnecessary burden for study participants given the change of the study to an open clinical trial. Adding physiological assessment and Simsensei to the post-treatment assessment will reflect symptom changes due to treatment.

Amendment 3: Add option to receive treatment sessions daily as part of Emory Healthcare Veterans Program 2 week Intensive Outpatient Program (IOP), which often includes veterans/service members who reside outside of Georgia. Veterans will complete treatment sessions daily for two weeks (10 business days) consistent with the current MST and IOP treatment protocols.

Amendment 3 Rationale: Currently participants interested in Emory Healthcare Veterans Program outpatient services are offered participation in the BraveMind study. Individuals residing outside the Atlanta metro area or Georgia have also expressed interest in participation. Offering this service will allow a greater number of veterans to engage in the treatment study. IOP participants will be compensated for travel, lodging, and food expenses through another grant regardless if they participate in this study or not.

Amendment 3a: All IOP participants will complete the pre-assessment and post-treatment assessment while onsite for treatment. IOP participants will complete the 3 month follow-up either onsite or remotely per participant preference. If study funding is available, long-distance participants will be reimbursed for travel in order to complete the 3 month follow-up assessment onsite. If the assessment is conducted remotely, participants will complete interview measures via phone and self-report measures via mail or email per participant preference. The remote assessment will not include the psychophysiological assessment/Simsensei.. If the 3 month follow-up assessment is completed onsite, the participants will complete both the interview measures and psychophysiological assessment/Simsensei onsite.

Amendment 3a Rationale: IOP participants will complete treatment two weeks following the pre-assessment and will complete the post-treatment assessment, including psychophysiological

assessment/Simsensei onsite after the final treatment session. To reduce additional travel burden to the IOP participants, we will not require participants to return for an onsite assessment for the 3 month follow up assessment time point.

Amendment 3b: For IOP participants only, 1) eliminate $20 reimbursement for treatment sessions, 2) retain $50 reimbursement for all onsite assessments that include psychophysiological assessment/Simsensei, 3) provide $20 reimbursement for assessments that are conducted remotely to reflect reduced time/travel required for the assessment while funding lasts.

Amendment 3b Rationale: As part of the intensive outpatient program, veterans' lodging and food expenses are covered during the course of their treatment through a separate grant. They commit their days to the treatment program. Reimbursement for travel/time for appointments is unnecessary for these patients, as they already are onsite for the purpose of treatment. Similarly, with the elimination of psychophysiological assessment/Simsensei for the remote assessments, the time/travel commitment is lower than that required for onsite assessment points.

APPENDIX 4: Journal of Anxiety Disorders Abstract Submission

Virtual Reality Exposure Therapy for Military Sexual Trauma: An Open Clinical Trial

Laura Loucks[1], Carly Yasinski[1], Jessica Maples[1], Skip Rizzo[2] & Barbara O. Rothbaum[1]

Emory University[1]

University of Southern California[2]

Experiencing military sexual trauma (MST) can have a debilitating impact on one's mental and physical wellbeing and may result in posttraumatic stress disorder (PTSD). With avoidance as a hallmark symptom of PTSD, engaging in exposure-based PTSD treatment can be a challenge. Virtual Reality Exposure Therapy (VRET), an effective treatment for combat related PTSD, has potential to help MST survivors more actively engage with trauma memories during the treatment process by virtually providing the context of the assault. VRET may also promote acceptability and reduce stigma regarding psychotherapy by way of its delivery using technology with which veterans may feel more comfortable. This ongoing treatment study (enrollment concluding end of May 2017) examined the feasibility and efficacy of VRET in the treatment of PTSD due to MST. Current participants include 11 veterans (2 male). Treatment included a minimum of 6 and maximum of 12 VRET sessions. Participants completed pre, post, and 3-month follow-up assessments to assess ongoing treatment effect. Psychophysiological data, including cortisol, skin conductance, heart-rate and startle response, were collected at each assessment point. Analyses will examine change in PTSD and depressive symptoms and physiological data across assessment points. It is hypothesized that VRET will be safely deliverable as evidenced by treatment drop-out rates similar to existing PTSD treatment, and will be effective as evidenced by clinically meaningful reductions in 1) PTSD and depression symptoms, and 2) physiological reactivity scores.

APPENDIX 5: Recruitment Efforts

Detailed MST recruitment efforts through 8/12/2016 (enrollment conclusion date):

1. Advertisements/Social Media:
   - Emory Healthcare on hold message advertisement
   - Digital display adds on various news and veteran organization websites (6/2016-8/2016)
     o Advertising outcomes:
       ▪ Impressions: 2,122,524
       ▪ Clicks: 5,969
       ▪ Click Thru Rate: .28%
       ▪ Total visits to our landing page from ads: 2,746
   - Study advertising on Facebook
     o Advertising outcomes:

	MST Facebook Campaign- Launched 6/9			
	Jun-16	Jul-16	Aug-16	YTD
Reach	118,943	140,191	122,239	381,373
Link Clicks	28,937	44,130	30,781	103,848
Likes	25	4	11	40
Shares	4	4	2	10
Comments	2	0	0	2
CTR	6.06%	6.11%	5.29%	

2. Websites Links:
   - MST recruitment statement on the Emory Psychiatry Clinical Research Trial webpage: http://www.psychiatry.emory.edu/research/clinical_trials/ptsd/rothbaum_MilitarySexTrauma.html
   - Emory Healthcare Veterans Program Webpage: http://emoryhealthcare.org/veterans-program/conditions/mst.html?gclid=CjwKEAiAmNW2BRDL4KqS3vmqgUESJABiiwDTuYEOPAeQ6kmQZ911nKmGa0NpNfjrTK71_InAArsdGxoCRYPw_wcB

3. Community and Provider Outreach:
   - Follow up outreach with Atlanta Army's SHARP (Sexual Harassment/Assault Response & Prevention) Program (5/27/16)
   - Phone contact with the following Veterans organizations regarding MST study opportunities:
     o Veterans Empowerment Organization (7/26/16)
     o Georgia Department of Veterans Services (7/26/16)
     o Wounded Warrior Project, Atlanta Offices (7/27/16)
     o USA Cares, Georgia Chapter (7/27/16)
   - Atlanta VAMC
     o Monthly email communication with Trauma Recovery Program MST and PE/CPT Team
     o Monthly email outreach with General Mental Health Clinics in Atlanta Area

4. Flyer/Information Distribution:
   - Veteran outreach coordinators consistently presented MST Study during weekly outreach efforts at Veteran and Military Events
     o Veterans Day and Memorial Day parades, Pat Tillman Memorial Day 5k Run/Walk (5/30/16)

- o Gary Sinise Concert in Pemberton Place, Atlanta Aquarium (6/18/2016)
- o Georgia National Guard workshop with Kennesaw State University (6/29/16)
- o Georgia National Guard Resource Fair at Joint Force Headquarters (6/30/2016)
- o Revival 4th of July Veteran Appreciation Dinner (7/4/16)
- o Black Veterans Helping Veterans Inc (7/7/2016)
- o Rome Braves Game (7/9/16)
- o Community Awareness Day (7/23/16)
- o No Barriers Expedition (7/24/16-7/30/16)
- o Veterans Empowerment Organization 8th Anniversary Celebration (7/28/16)
- o Uniting Forces at the Carter Center (7/29/16)
- o 2016 Disabled American Veteran National Conference Atlanta Hyatt Regency Peachtree Street (7/31/16-8/3/16)
- o VETLANTA Q3 Summit (8/11/16)
- o Monthly: Red Cross Veteran Outreach
- o Monthly: Gwinnett Coalition for Health & Human Services
- Flyers posted throughout Atlanta metro and surrounding area businesses

5. Recruitment through Emory Healthcare's Veterans Program
- Eligible veterans with MST who enroll in Emory Healthcare Veterans Program offered the MST study as a treatment option

APPENDIX 6: Case Vignettes

Given the small sample size, individual case vignettes are presented for all participants who enrolled in the study (N = 15). Each vignette provides a brief overview of demographics, participation in the study, and outcomes as available.

Participant 1: Discontinued Study

Participant 1 was a 72-year-old, black, male Navy veteran. At the time of the study he was divorced and retired. He reported MST due to being sexually assaulted by a fellow sailor while on a naval ship. In addition to PTSD, he met DSM-5 criteria for major depressive disorder. The veteran was assigned to the waitlist condition, and after the 6-week waitlist period, the veteran reported that he was unable to complete the study at the time due to health problems, including a surgery. He expressed ongoing interest; however, he was unreachable after the original follow-up contact and ultimately lost to the study. Pre-assessment scores were as follows: CAPS severity = 30, PCL-5 = 53. He did not complete the PHQ-9.

Participant 2: Study Completer

Participant 2 was a 44-year-old, white, female Navy veteran, who was honorably discharged at a rank of E3. She had no deployments. At the time of the study, she was married and identified as a house-wife. She reported MST due to being sexually assaulted by a fellow sailor while on a date. In addition to PTSD, she met DSM-5 criteria for major depressive disorder, panic disorder, agoraphobia, and social anxiety disorder. She reported a history of childhood sexual, emotional, and physical abuse. Participant 2 was randomized to the treatment condition and completed five treatment sessions to address MST; thus, she did not complete a full dose of treatment.

During treatment, the veteran reported significant avoidance, including some dissociation, during VR exposures, and little reduction in subjective distress. Additionally, she reported an increase in re-experiencing symptoms and reported the belief that exposure felt disruptive to her life.
From pre-treatment to 3-month follow-up assessments, there was no change in self-reported PTSD or depressive symptoms and no change in self-reported PTSD symptoms across treatment sessions. However, there was a decline in clinician assessed PTSD symptoms from pre-treatment and post-treatment assessments to the 3-month follow-up (see Figures 1 and 2). At the 3-month follow-up, the veteran rated herself as "minimally worse" on the clinical global impression scale.

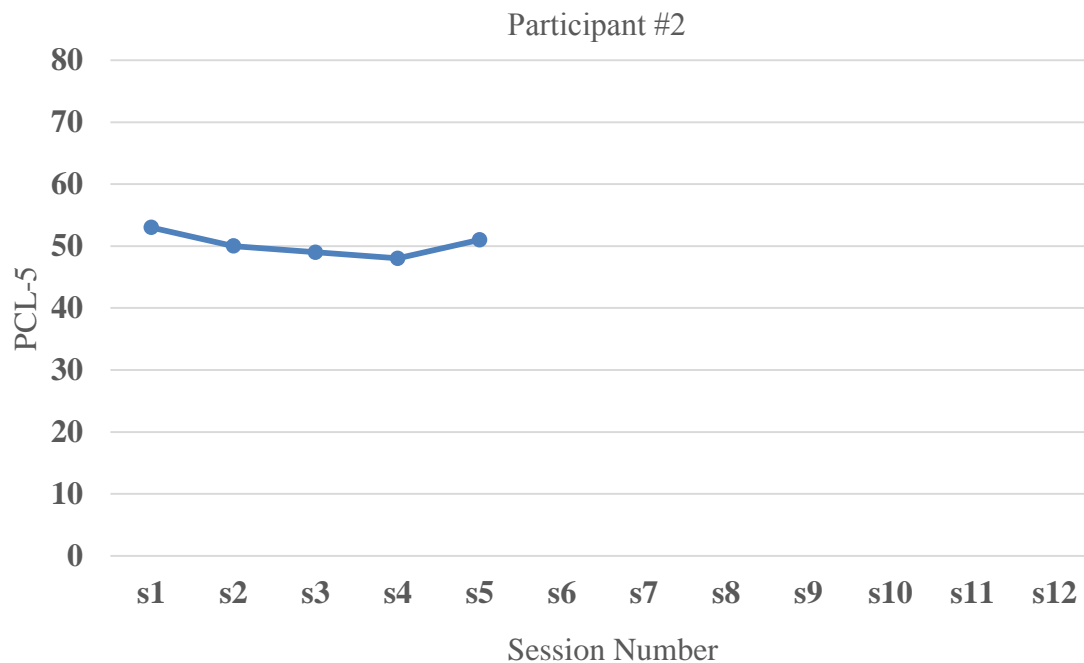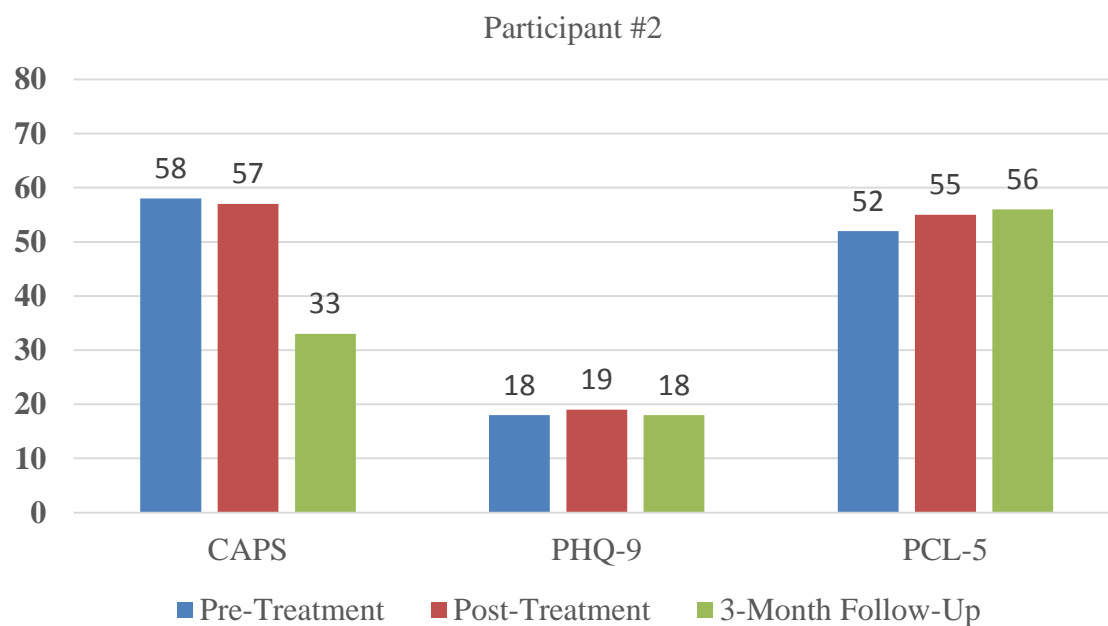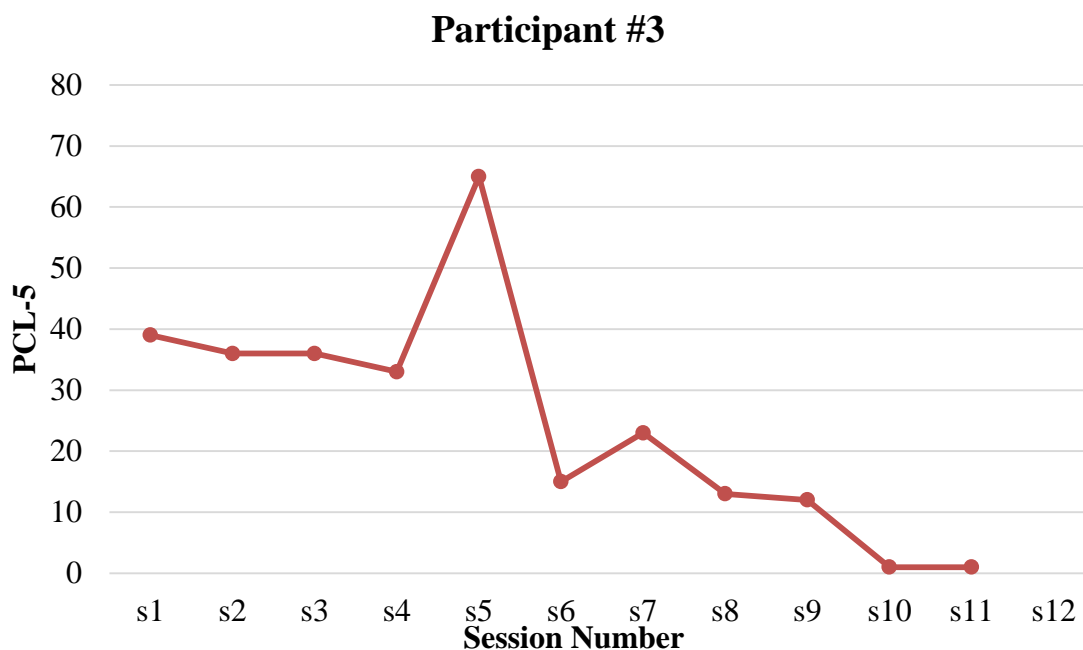*Figure 1. Participant 2 PCL-5 scores across treatment sessions.*

Participant #2

Figure 2. Participant 2 pre-treatment, post-treatment, and 3-month follow-up assessment scores.

Participant #2

Participant 3: Treatment Completer

Participant 3 was a 54-year-old, white, female, Air Force veteran, who retired from the military at a rank of E6. She deployed as part of Desert Storm. At the time of the study, she was divorced and employed full-time. She reported MST due to being sexually assaulted by her ex-boyfriend after he broke into her base housing. She did not meet criteria for any other DSM-5 disorder. She reported a history of childhood sexual abuse. Participant 3 was randomized to the treatment condition and completed eleven treatment sessions to address MST; thus, she completed a full dose of treatment.

Participant 3 attended sessions regularly and engaged well in virtual reality exposures. She reported large decreases in subjective distress during exposures over treatment.

From pre-treatment to 3-month follow-up assessments, there were significant reductions in PTSD and depressive symptoms as well as self-reported PTSD symptoms across treatment sessions (see Figures 3 and 4). At the 3-month follow-up, the veteran rated herself as "very much improved" on the clinical global impression scale.

Figure 3. Participant 3 PCL-5 scores across treatment sessions.

Participant #3

Figure 4. Participant 3 pre-treatment, post-treatment, and 3-month follow-up assessment scores.

Participant #3

Assessment	Pre-Treatment	Post-Treatment	3-Month Follow-Up
CAPS	40	3	6
PHQ-9	12	3	2
PCL-5	32	1	2
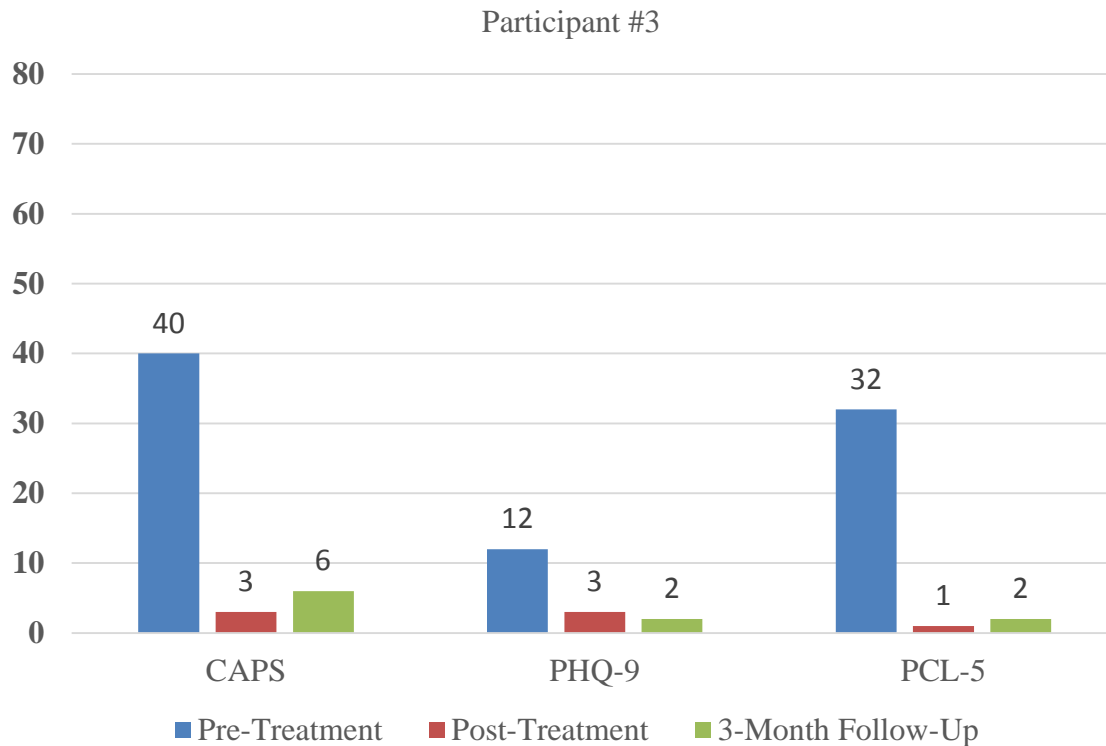
Participant 4: Discontinued study

Participant 4 was a 60-year-old, black, female, Air Force veteran, who retired from the military at a rank of O3. At the time of the study, she had never been married and was not seeking employment. She reported MST due to unwanted sexual contact by fellow service members. In addition to PTSD, she met DSM-5 criteria for major depressive disorder, agoraphobia, and generalized anxiety disorder. Participant 4 was randomized to the waitlist condition and discontinued the pre-assessment process before completing self-report measures. During a follow-up phone call, she expressed that she did not want to confront avoided memories and was not ready to engage in treatment at this time. She discontinued study engagement. Pre-assessment scores were as follows: CAPS severity = 46. She did not complete the PCL-5 or the PHQ-9.

Participant 5: Treatment Completer

Participant 5 was a 39-year-old, black, female, Navy veteran, who was honorably discharged from the military at a rank of E4. At the time of the study, she had never been married and was employed part-time. She reported MST due to being raped by a friend who was a higher-ranking sailor while deployed. She also reported a second MST. In addition to PTSD, she met DSM-5 criteria for major depressive disorder, agoraphobia, and generalized anxiety disorder. She denied a history of childhood abuse. Participant 5 was randomized to the treatment condition and completed twelve treatment sessions to address MST; thus, she completed a full dose of treatment.

Participant 5 attended sessions regularly and engaged well in virtual reality exposures. She reported large decreases in subjective distress during exposures across treatment.

From pre-treatment to 3-month follow-up assessments, there were significant reductions in PTSD symptoms, and depressive symptoms decreased from the severe range to the moderately severe range. Self-reported PTSD symptoms also declined across treatment sessions (see Figures 5 and 6). At the 3-month follow-up, the veteran rated herself as "much improved" on the clinical global impression scale.

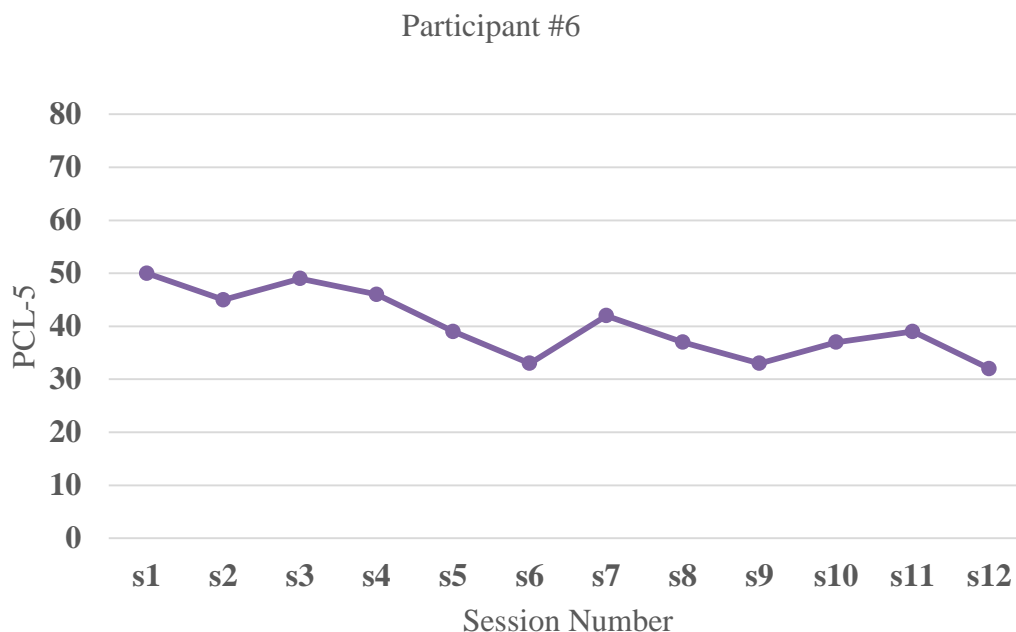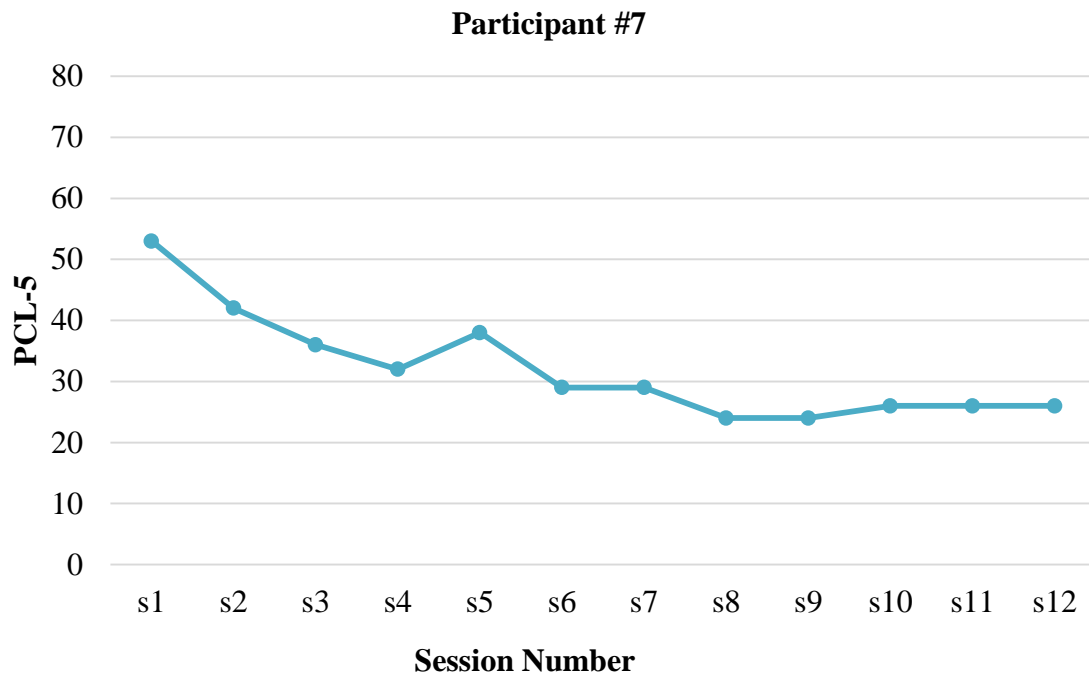*Figure 5. Participant 5 PCL-5 scores across treatment sessions.*
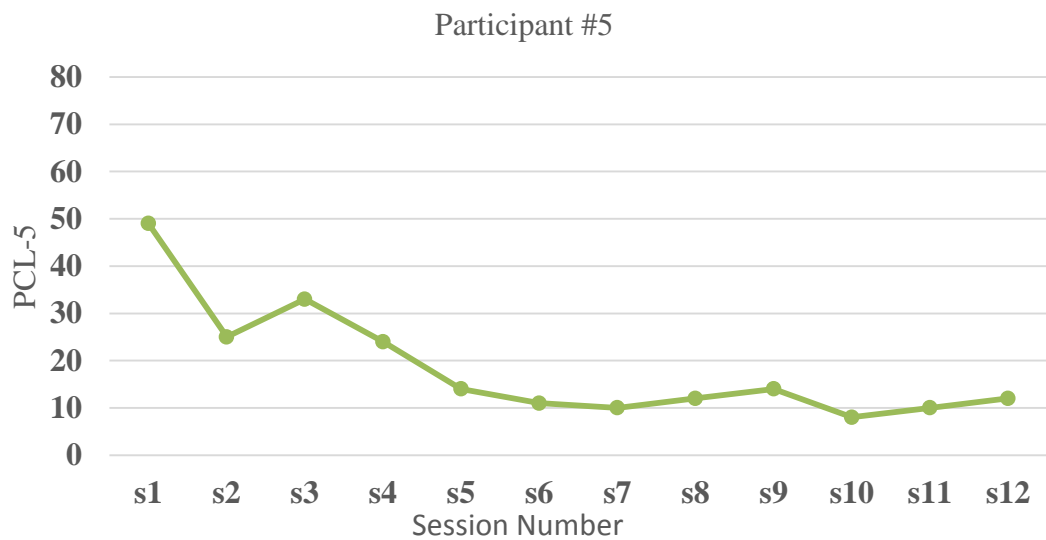
Figure 6. Participant 5 pre-treatment, post-treatment, and 3-month follow-up assessment scores.
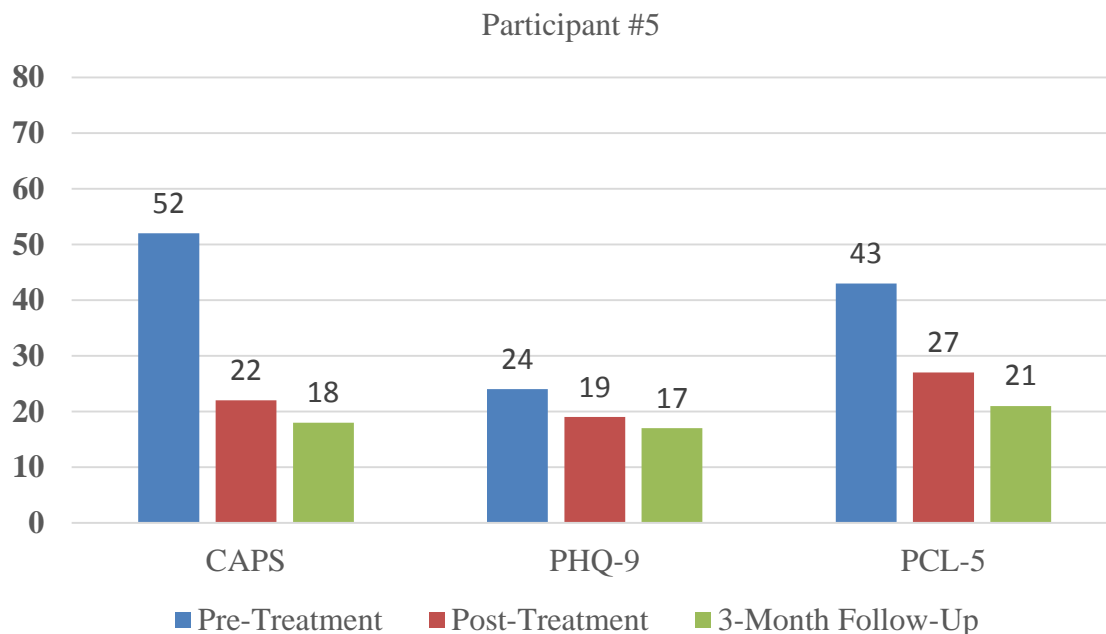
Participant 6: Treatment Completer

Participant 6 was a 53-year-old, black, female, Army veteran, who was honorably discharged from the military at a rank of E4. At the time of the study, she was widowed and was employed full-time. She reported MST due to being raped by another soldier in his barracks. She reported a second MST. She did not meet criteria for any other DSM-5 disorder. She denied a history of childhood abuse. Participant 6 was randomized to the waitlist condition and completed twelve treatment sessions to address MST; thus, she completed a full dose of treatment.

Participant 6 attended sessions regularly and engaged well in virtual reality exposures and reported moderate reductions in subjective distress. She had difficulty engaging in the in vivo exposures and in eliminating safety behaviors throughout treatment.

From pre-treatment to 3-month follow-up assessments, there was little change in PTSD and depressive symptoms; however, self-reported PTSD symptoms declined to subthreshold levels of PTSD from the initial to final treatment session (see Figures 7 and 8). Of note, the veteran discontinued venlafaxine and prazosin prior to treatment and against recommendations. At the 3-month follow-up, the veteran rated herself as "much improved" on the clinical global impression scale. She reported increased social engagement, including traveling with friends.

Figure 7. Participant 6 PCL-5 scores across treatment sessions.

Participant #6

Figure 8. Participant 6 pre-treatment, post-treatment, and 3-month follow-up assessment scores.
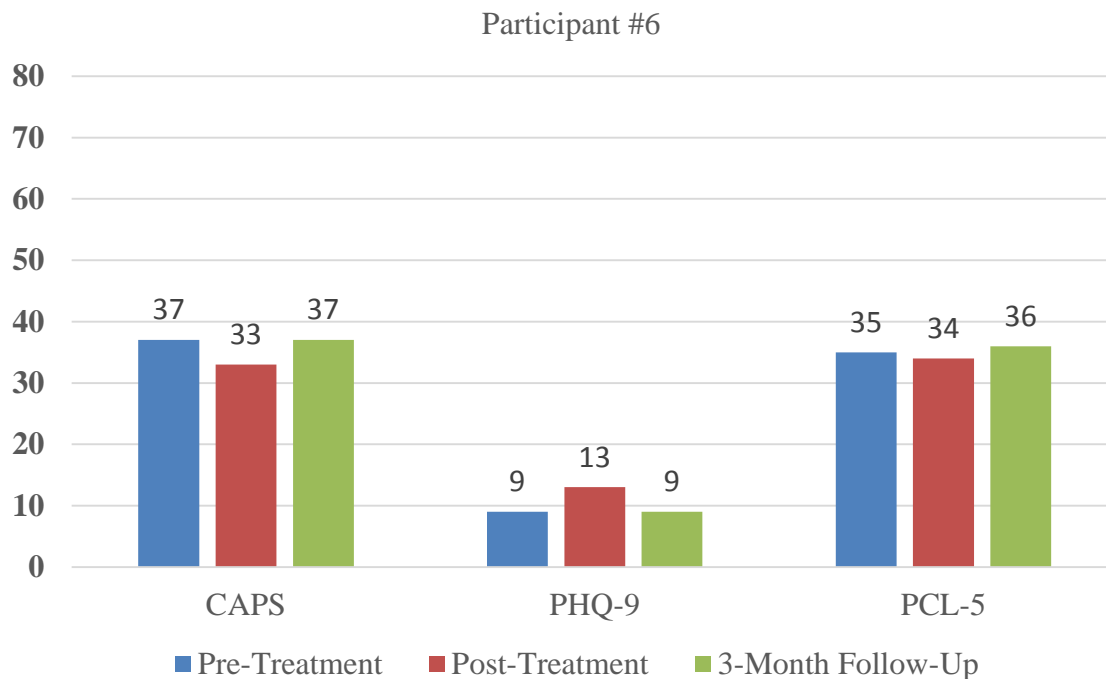
Participant 7: Treatment Completer

Participant 7 was a 38-year-old, black, female, Army veteran, who was honorably discharged from the military at a rank of E4. She deployed once to Iraq and once to Afghanistan. At the time of the study, she was never married and was employed part-time. She reported MST due to being sexually assaulted by a fellow soldier she was dating while on R&R from Iraq. She did not meet criteria for any other DSM-5 disorder. She endorsed combat trauma as well as childhood sexual abuse. Participant 7 was randomized to the treatment condition and completed twelve treatment sessions to address MST; thus, she completed a full dose of treatment.

Participant 7 did not consistently attend sessions; however, she was engaged during sessions and completed homework practice. She reported a moderate reduction in subjective stress during VR exposures.

From pre-treatment to 3-month follow-up assessments, there were significant reductions in PTSD symptoms, and depressive symptoms declined from the moderately severe to moderate range. Self-reported PTSD symptoms also declined across treatment sessions (see Figures 9 and 10). At the 3-month follow-up, the veteran rated herself as "much improved" on the clinical global impression scale.

Figure 9. Participant 7 PCL-5 scores across treatment sessions.

Participant #7

Figure 10. Participant 7 pre-treatment, post-treatment, and 3-month follow-up assessment scores.
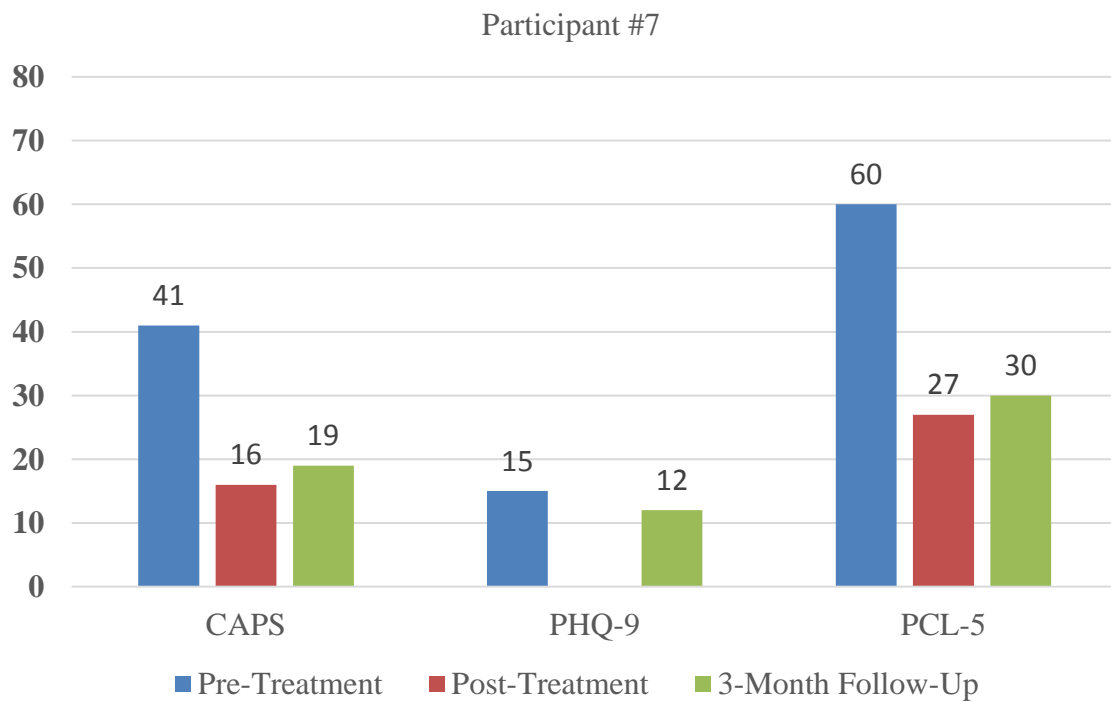
Participant #7

Participant 8: Treatment Completer

Participant 8 was a 45-year-old, black, female, Navy veteran, who was honorably discharged from the military at a rank of E3. She never deployed. At the time of the pre-treatment assessment, she was married and employed full-time. Prior to starting treatment she lost her job. She reported MST due to being sexually assaulted by a Marine she met at a nightclub. In addition to PTSD, she met DSM-5 criteria for major depressive disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, and substance use disorder within the past twelve months. She endorsed combat trauma as well as childhood sexual abuse. Participant 8 was randomized to the treatment condition and completed ten treatment sessions to address MST; thus, she completed a full dose of treatment.

Participant 8 reported minimal reduction in subjective distress during VR exposures. Homework completion and engagement were variable. During last few sessions, participant reported ongoing verbal/emotional abuse from husband and chose to discontinue the study, as MST was not her primary concern. Also near the end of treatment, she stated that main motivation for engagement was money.

From pre-treatment to 3-month follow-up assessments, there was little change in PTSD and depressive symptoms. Self-reported PTSD symptoms also did not change significantly across treatment sessions (see Figures 11 and 12). At the 3-month follow-up, the veteran rated herself as "much worse" on the clinical global impression scale.

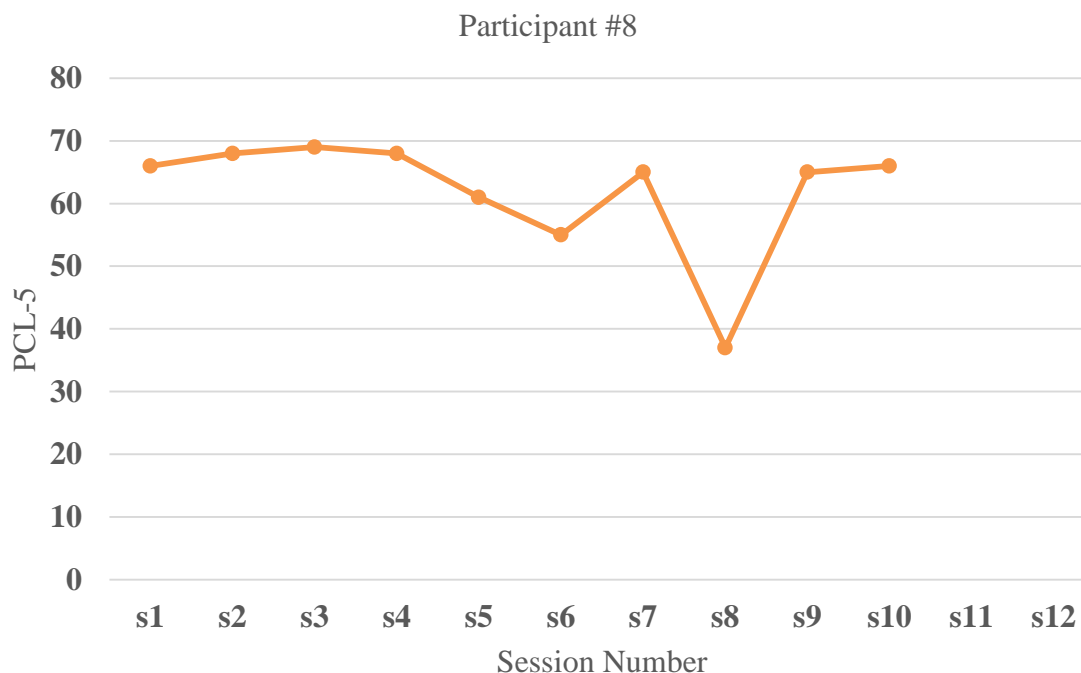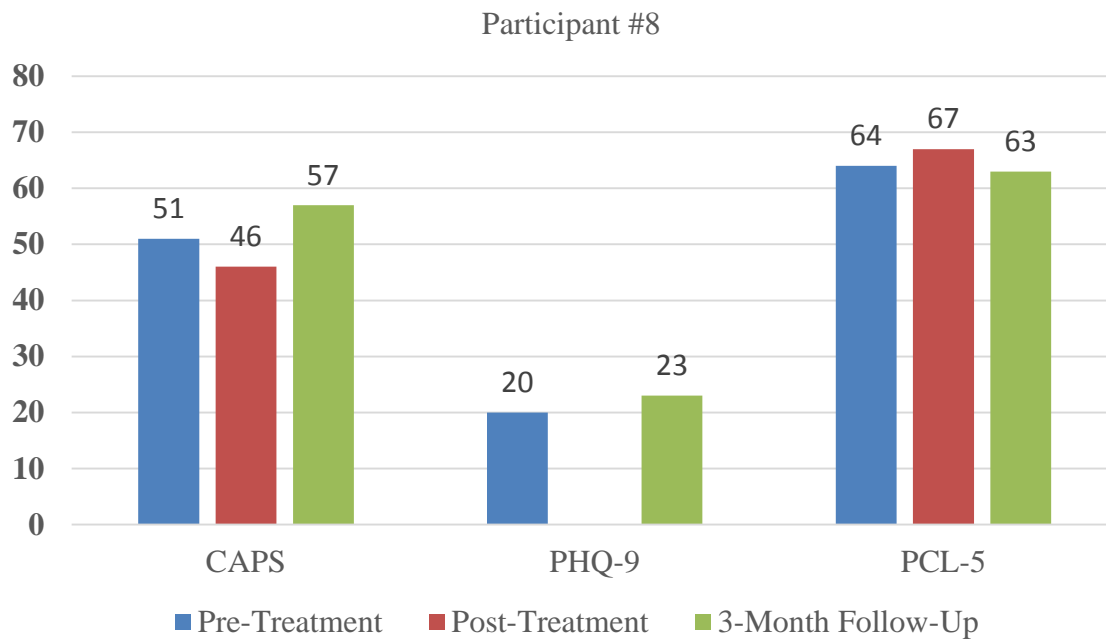*Figure 11. Participant 8 PCL-5 scores across treatment sessions.*

Figure 12. Participant 8 pre-treatment, post-treatment, and 3-month follow-up assessment scores.

Participant 9: Study Completer

Participant 9 was a 37-year-old, black, female Navy veteran, who was honorably discharged at a rank of E5. She was deployed once to Iraq and once to Afghanistan. At the time of the study, she had never been married and was a student. She reported MST due to being raped in her residence by a fellow solder who was a friend. In addition to PTSD, she met DSM-5 criteria for major depressive disorder. She reported a history of childhood physical abuse. Participant 9 was randomized to the treatment condition and completed four treatment sessions to address MST; thus, she did not complete a full dose of treatment.

During treatment, the veteran was engaged in sessions and partially engaged in homework exercises. She reported some ongoing avoidance and continued safety behaviors. In the middle of treatment, the veteran had surgery, which resulted in a two-week break from sessions. Additionally, she returned to school. The veteran was increasingly difficult to schedule for sessions and she canceled frequently. The study team and veteran decided to discontinue treatment.

From pre-treatment to 3-month follow-up assessments, there were increases in self-reported PTSD and depressive symptoms and little change in clinician assessed PTSD symptoms. There were fluctuations in self-reported PTSD symptoms across treatment sessions (see Figures 13 and 14). At the 3-month follow-up, the veteran rated herself as "unchanged" on the clinical global impression scale.

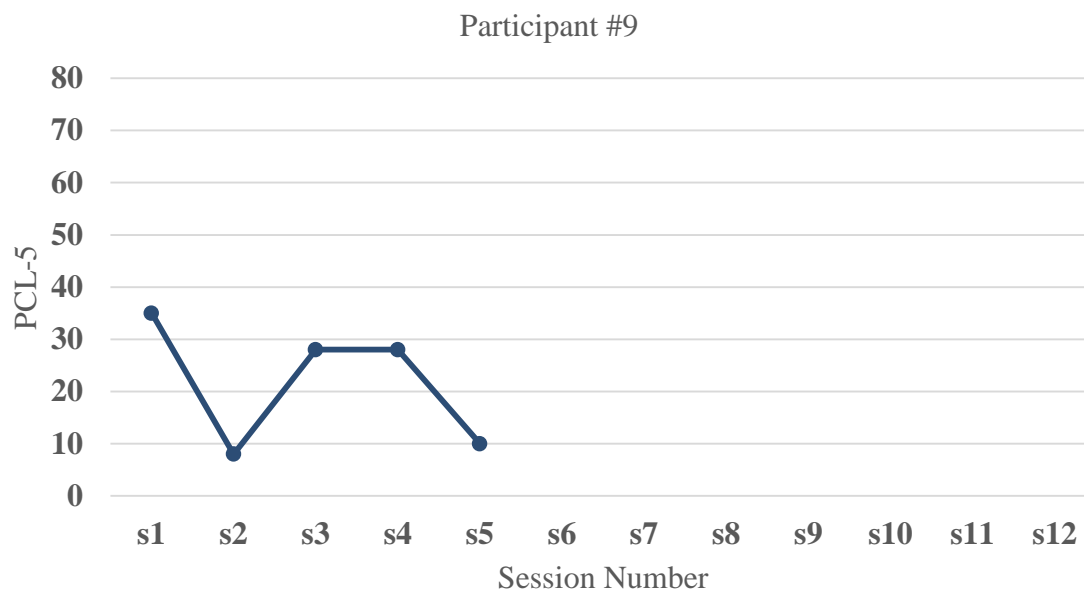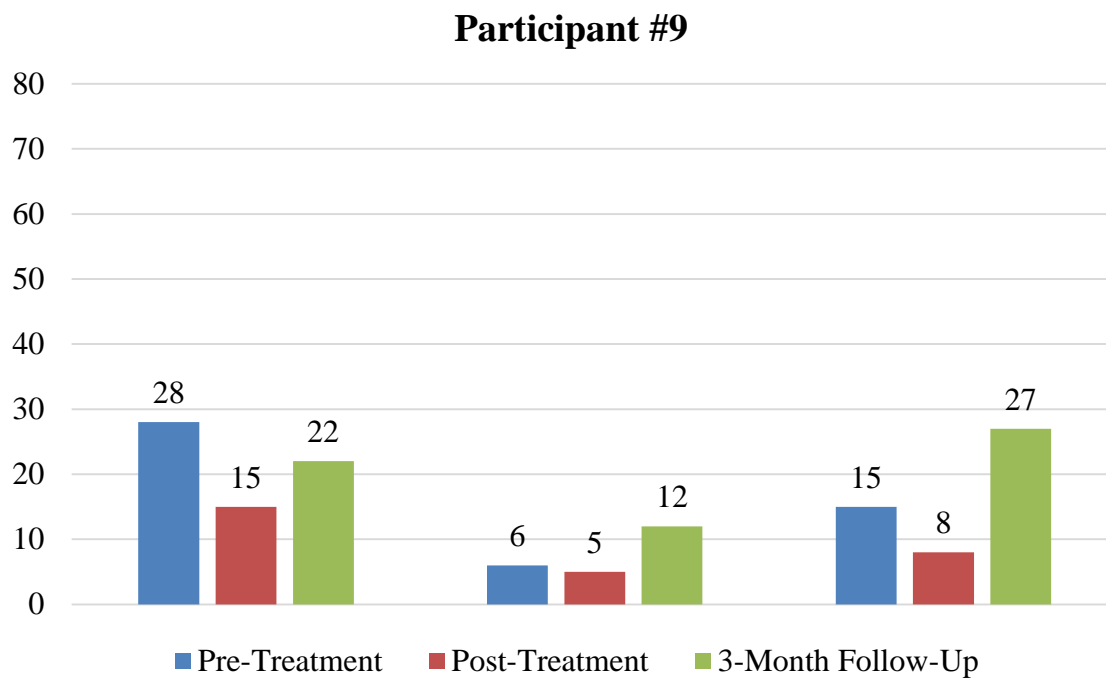*Figure 13. Participant 9 PCL-5 scores across treatment sessions.*

Figure 14. Participant 9 pre-treatment, post-treatment, and 3-month follow-up assessment scores.
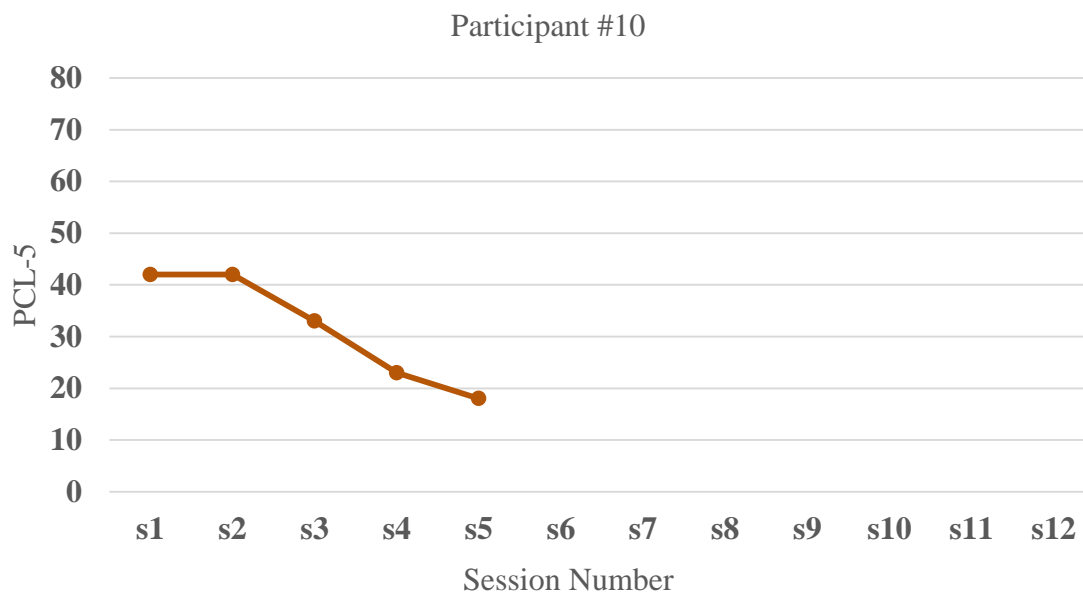
Participant 10: Discontinued study

Participant 10 was a 39-year-old, black, male Navy veteran, who was honorably discharged at a rank of E5. He was deployed twice in support of OIF. At the time of the study, he was married and employed part-time. He reported MST due to awakening to a fellow sailor lying on the participant's back and later learning the same sailor had assaulted another individual. He did not meet criteria for any other DSM-5 disorder. Via self-report, the veteran endorsed possible childhood sexual and physical abuse. Participant 10 participated in the study as part of the open clinical trial and completed five treatment sessions to address MST; thus, he did not complete a full dose of treatment.

During treatment, the veteran appeared to have low insight in his own symptoms and how MST may have affected him. Over the course of treatment the veteran reported subjective improvement; however, attendance was variable. After many no-shows and cancellations for the planned final session, the study team decided to end patient's participation. The veteran did not complete a post-treatment assessment and is being scheduled for a 3-month follow-up assessment.

Pre-treatment assessment scores were as follows: CAPS severity = 28, PCL-5 = 45, PHQ-9 = 12. There were declines in self-reported PTSD symptoms across treatment sessions (see Figure 15), and at the final session, the veteran rated himself as "much improved" on the clinical global impression scale.

*Figure 15. Participant 10 PCL-5 scores across treatment sessions.*

Participant 11: Discontinued study

Participant 11 was a 35-year-old, black, female Army veteran, who was honorably discharged at a rank of E2. She was never deployed. At the time of the study, she had never been married and was employed full-time. She reported MST due to being sexually assaulted in her base housing after a fellow soldier she used to date showed up at her door. In addition to PTSD, she met DSM-5 criteria for panic disorder and agoraphobia. She reported a history of childhood emotional and sexual abuse. Participant 11 participated in the study as part of the open clinical trial and completed five treatment sessions to address MST; thus, she did not complete a full dose of treatment.

During treatment, the veteran reported significant life stressors, including a tumultuous family life, as she struggled to raise her son who was the product of the rape. She continued to report desire to dropout and did not consistently complete homework practice. Additionally, she demonstrated severe emotion dysregulation and active suicidal ideation. The veteran was encouraged to remain with her VA therapist and begin DBT through the VA.

There were increases in self-reported PTSD symptoms across treatment sessions (see Figure 16). At the final session, the veteran rated herself as "much worse" on the clinical global impression scale.

*Figure 16. Participant 11 PCL-5 scores across treatment sessions.*
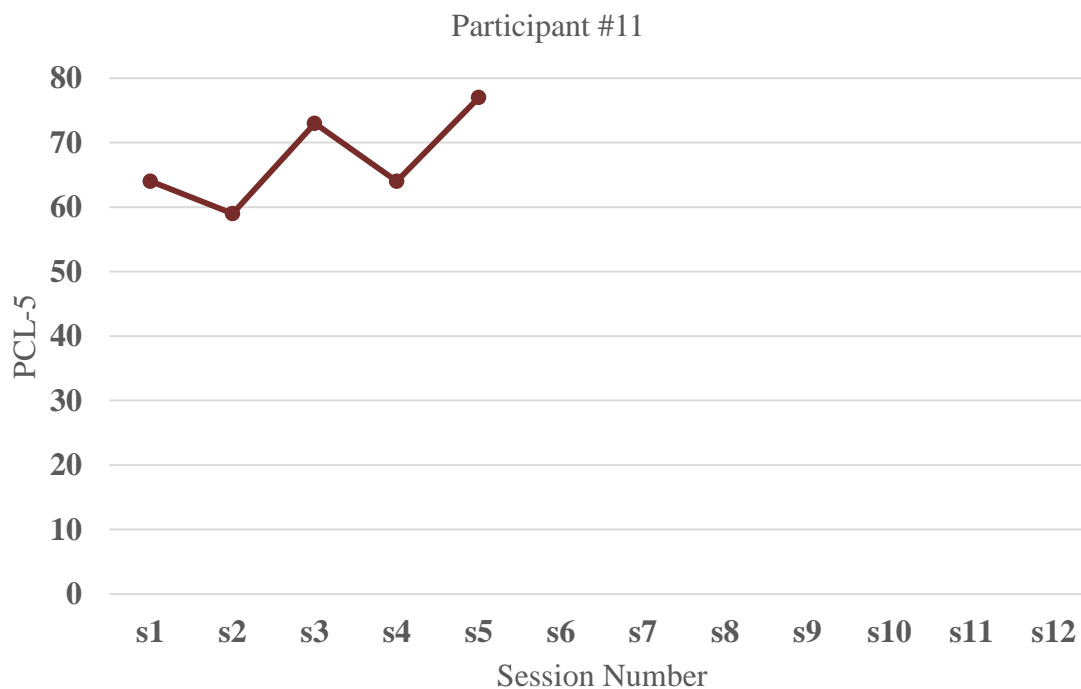
Participant 12: Study Completer

Participant 12 was a 48-year-old, white, female Air Force veteran, who was honorably discharged at a rank of E6. She was deployed once to Kuwait. At the time of the study, she was divorced and unemployed. She reported MST due to a subordinate airman forcing himself into her barracks and forcing her onto the bed. She reportedly shouted and scared him away. In addition to PTSD, she met DSM-5 criteria for major depressive disorder. She reported a history of childhood emotional and sexual abuse as well as harsh punishment. Participant 12 participated in the study as part of the open clinical trial and as part of the Emory Healthcare Veterans Program 2-week Intensive Outpatient Program (IOP). She completed the equivalent of 5 treatment sessions to address MST; thus, she did not complete a full dose of treatment.

During treatment, the veteran was engaged in sessions, completed homework, and reported declines in subjective distress. Between the 3rd and 4th treatment sessions, the veteran presented to the VA emergency department to obtain refills in pain medications for fibromyalgia. At the ED, she reportedly became distressed and was voluntarily hospitalized overnight for monitoring. After the event, the participant reported difficulty re-engaging in treatment and considered leaving the program. Ultimately, she decided to complete prolonged exposure therapy without the use of virtual reality, which reportedly gave her a headache. The veteran is scheduled for the 3-month post treatment assessment.

From the pre-treatment to post-treatment assessments, there were decreases in self-reported PTSD and depressive symptoms and little change in clinician-assessed PTSD symptoms. There were declines in self-reported PTSD symptoms across treatment sessions (see Figures 17 and 18). Additionally, psychophysiological indicators of distress, including startle, heart rate, and skin conductance, significantly declined from pre-treatment to post treatment assessment (see Figure 19).

Figure 17. Participant 12 PCL-5 scores across treatment sessions.
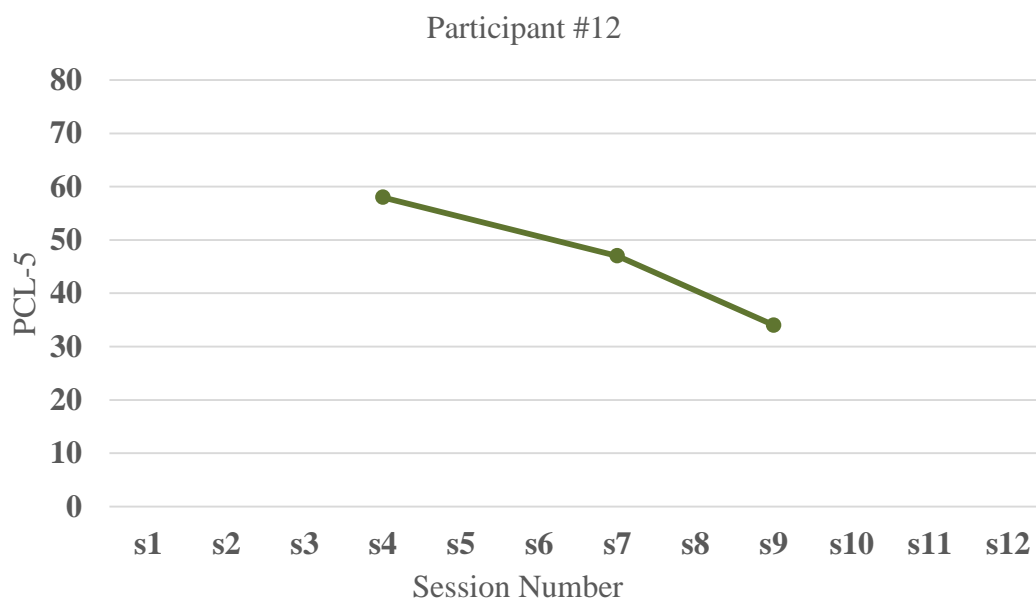
Note. During the IOP, the PCL-5 was administered after the 3rd, 6th, and 8th treatment sessions.

Figure 18. Participant 12 pre-treatment and post-treatment assessment scores.
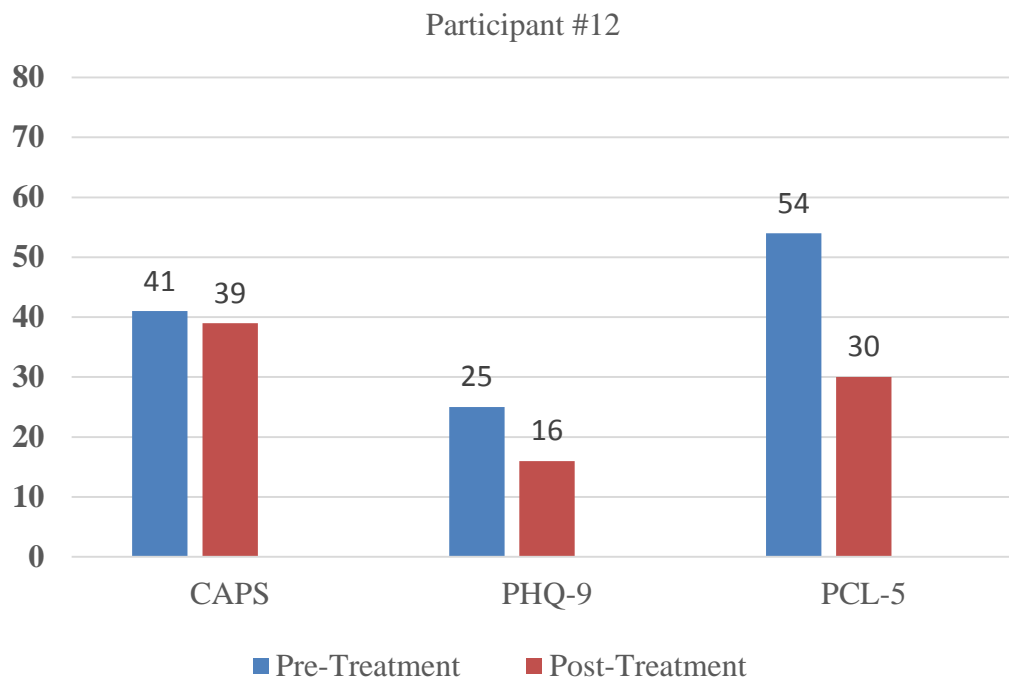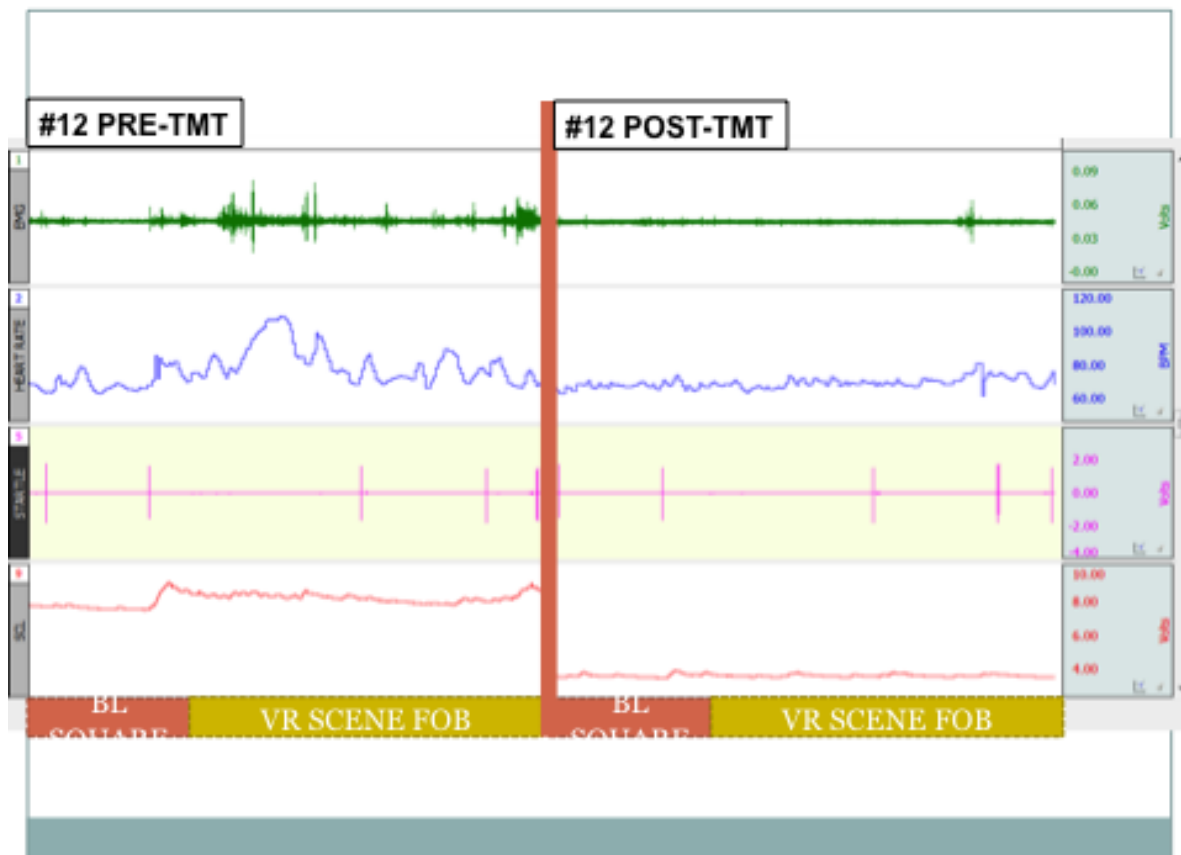

Participant #12

Figure 19. Participant 12 pre-treatment and post-treatment psychophysiological indicators of distress.

*Note.* From top row to bottom row: EMG, heart-rate, startle, skin conductance.

Participant 13: Treatment Completer

Participant 13 was a 41-year-old, white, female, Marine Corps veteran, who was honorably discharged from the military at a rank of E2. She was never deployed. At the time of the study, she married and was unemployed. She reported MST due to being raped by a fellow Marine. In addition to PTSD, she met DSM-5 criteria for major depressive disorder and generalized anxiety disorder. Participant 13 completed the study as part of the open clinical trial and as part of the Emory Healthcare Veterans Program 2-week Intensive Outpatient Program (IOP). She completed the equivalent of 9 treatment sessions to address MST; thus, she completed a full dose of treatment.

During treatment, the veteran was compliant and participated in VR and in vivo exposures daily. Overall she appeared to derive considerable benefit from treatment, as evidenced by her own report as well as therapist's observations. The veteran endorsed shifts in cognitions around the meaning and cause of the MST, and at the conclusion of her participation her symptoms appeared sub-clinical. Between the post-treatment and 3-month follow-up assessments, the veteran's husband reportedly left her unexpectedly. She reported increased distress related to the separation as well as a resurgence in PTSD symptoms.

From the pre-treatment to post-treatment assessments, there were significant reductions in self-reported PTSD symptoms, as well as reductions in clinician assessed PTSD symptoms. Self-reported PTSD symptoms also declined across treatment sessions (see Figures 20 and 21). At the 3-month follow-up, the veteran reported an increase in self-reported PTSD and depressive symptoms but clinician assessed PTSD symptoms were consistent with the post-treatment assessment. At the 3-month follow-up assessment, she rated herself as "minimally worse" on the clinical global impression scale, likely capturing general distress.

Figure 20. Participant 13 PCL-5 scores across treatment sessions.
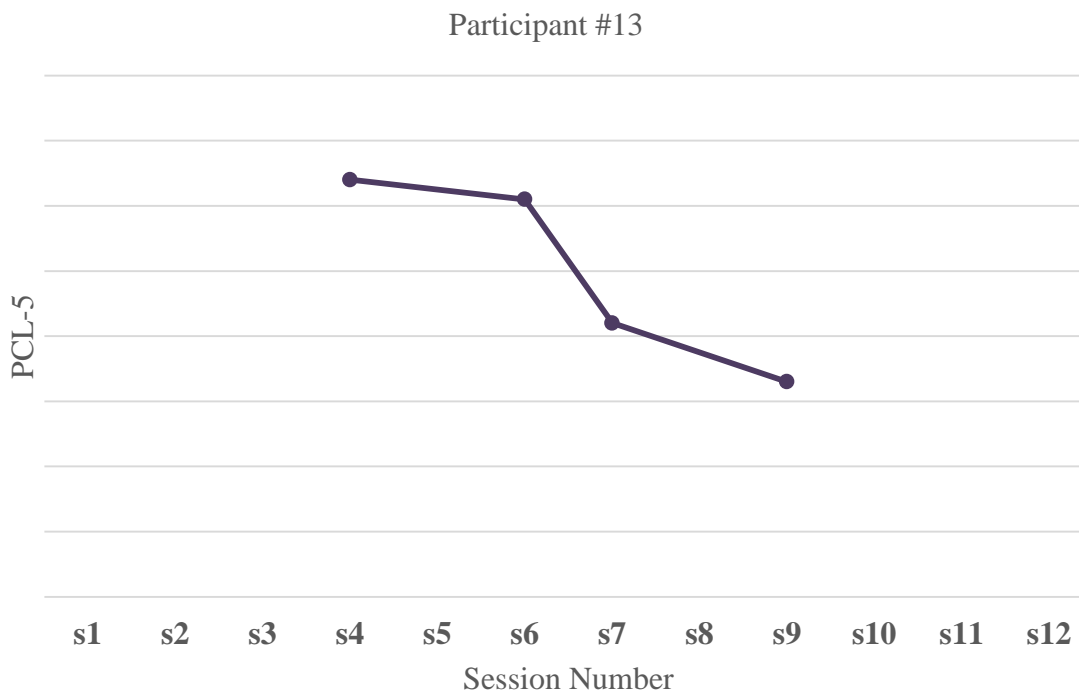
Participant #13

Note. During the IOP, the PCL-5 was administered after the 3rd, 5th, 6th, and 8th treatment sessions.

Figure 21. Participant 13 pre-treatment, post-treatment, and 3-month follow-up assessment scores.

Participant #13

Pre-Treatment Post-Treatment 3-Month Follow-Up
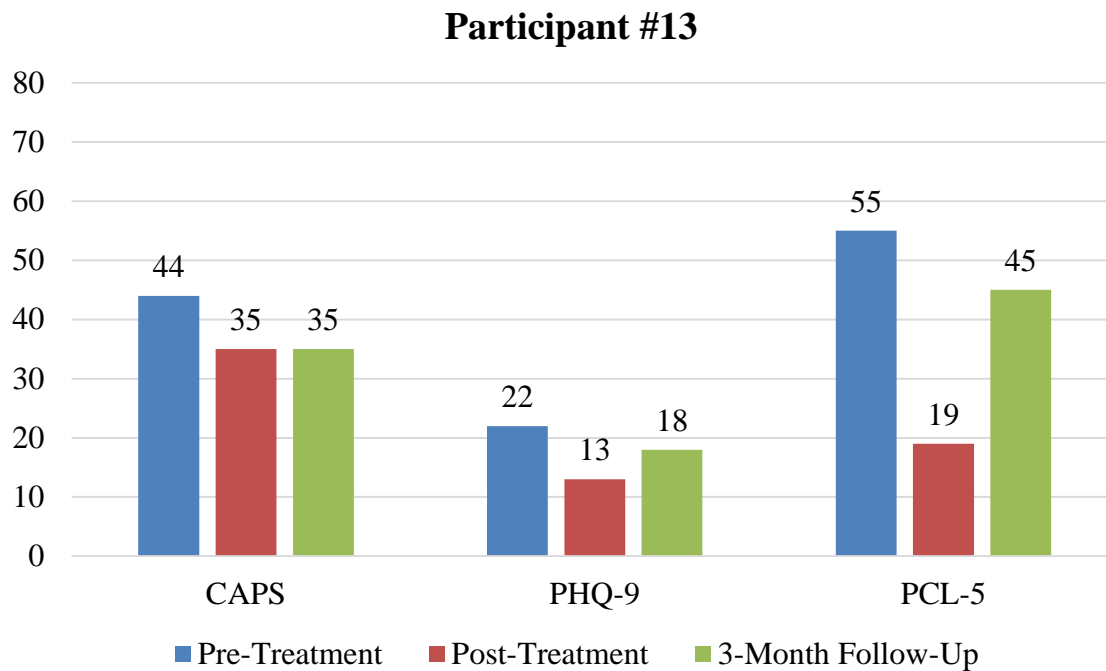
Participant 14: Treatment Completer

Participant 14 was a 53-year-old, black, male Marine Corps veteran, who was discharged in other than honorable conditions at a rank of E1. He deployed to Desert Storm. At the time of the study, he was divorced and unemployed. He reported MST due to a sexual assault by a noncommissioned officer. He did not meet criteria for any other DSM-5 disorder. He endorsed combat-related trauma. Participant 14 participated in the study as part of the open clinical trial and as part of the Emory Healthcare Veterans Program 2-week Intensive Outpatient Program (IOP). He completed the equivalent of 12 treatment sessions to address MST; thus, he completed a full dose of treatment.

During treatment the veteran was engaged in sessions and completed in vivo homework exercises. Midway through treatment, the veteran indicated he had not been compliant with listening to recordings of the virtual reality imaginal exposure. Subsquently, he completed all homework and subjective distress began to decline during in-session virtual reality exposures. Following treatment, the veteran indicated that had ongoing distress related to combat-trauma. The veteran is scheduled for the 3-month post treatment assessment.

From pre-treatment to post-treatment assessments, there were significant reductions in self-reported PTSD and depressive symptoms as well as reductions in clinician assessed PTSD symptoms. There were declines in self-reported PTSD symptoms across treatment sessions (see Figures 22 and 23). Additionally, psychophysiological indicators of distress, including heart rate and skin conductance, significantly declined from pre-treatment to post treatment assessment (see Figure 24). At the post-treatment assessment, participant 14 rated himself as "much improved" on the clinical global impression scale.

Figure 22. Participant 14 PCL-5 scores across treatment sessions.
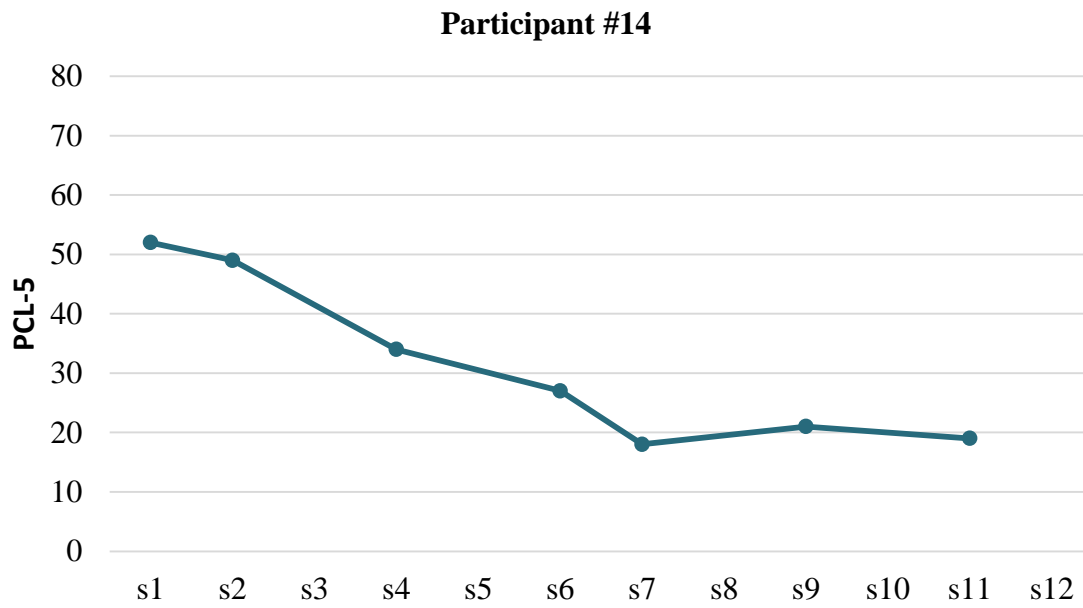
Participant #14

Note. During the IOP, the PCL-5 was administered after the 3rd, 5th, 6th, and 8th treatment sessions.

Figure 23. Participant 14 pre-treatment and post-treatment assessment scores.
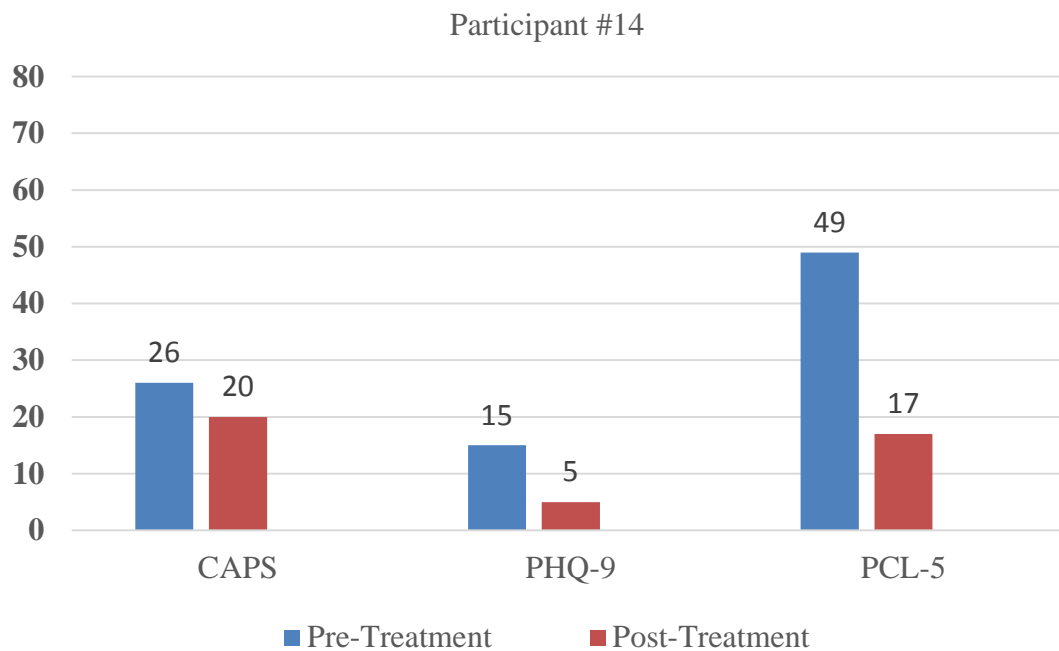
Participant #14

Figure 24. Participant 14 pre-treatment and post-treatment psychophysiological indicators of distress.

*Note*. From top row to bottom row: EMG, heart-rate, startle, skin conductance.

Participant 15: Treatment Completer

Participant 15 was a 38-year-old, male Navy veteran, who identified racially as "brown" with Hispanic heritage. He was honorably discharged at a rank of E4. He deployed to Egypt and Kuwait in support of OIF. At the time of the study, he was in a committed relationship and was on disability leave from work. He reported MST due to repeated sexual assault by a superior noncommissioned officer. In addition to PTSD, he met DSM-5 criteria for major depressive disorder, panic disorder, agoraphobia, and obsessive-compulsive disorder. He endorsed childhood sexual abuse, physical abuse, and physical neglect as well as a history of substance use disorder. Participant 15 participated in the study as part of the open clinical trial and as part of the Emory Healthcare Veterans Program 2-week Intensive Outpatient Program (IOP). He completed the equivalent of 11 treatment sessions to address MST; thus, he completed a full dose of treatment.

The veteran began treatment with some significant emotion dysregulation problems, including engagement in risky behaviors in response to emotions, but was highly motivated for treatment. He was very engaged and showed high emotional activation in initial sessions and demonstrated significant and relatively quick habituation. He showed a similar pattern with in vivo exposure. The veteran's maladaptive beliefs related to event greatly over the course of treatment. He is scheduled for the 3-month follow-up assessment.

From the pre-treatment to post-treatment assessments, there were significant reductions in self-reported and clinician-assessed PTSD symptoms. Depressive symptoms declined from the moderately severe to moderate range. There were declines in self-reported PTSD symptoms across treatment sessions (see Figures 25 and 26). Additionally, psychophysiological indicators of distress, including startle and skin conductance, significantly declined from pre-treatment to post treatment assessment (see Figure 27). At the post-treatment assessment, he rated himself as "much improved" on the clinical global impression scale.

Figure 25. Participant 15 PCL-5 scores across treatment sessions.
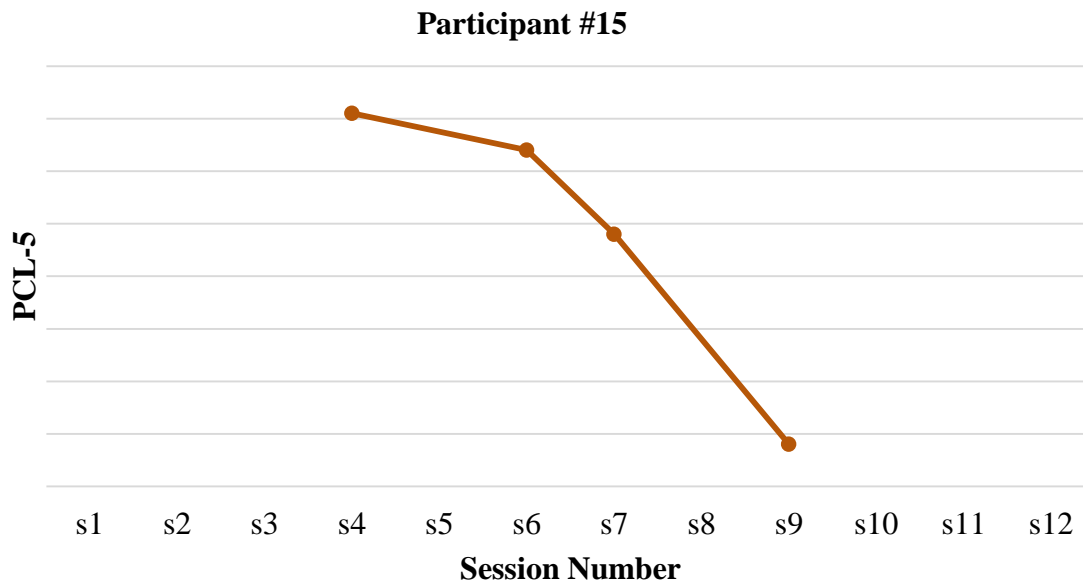
Participant #15

Note. During the IOP, the PCL-5 was administered after the 3rd, 5th, 6th, and 8th treatment sessions.

Figure 26. Participant 15 pre-treatment and post-treatment assessment scores.
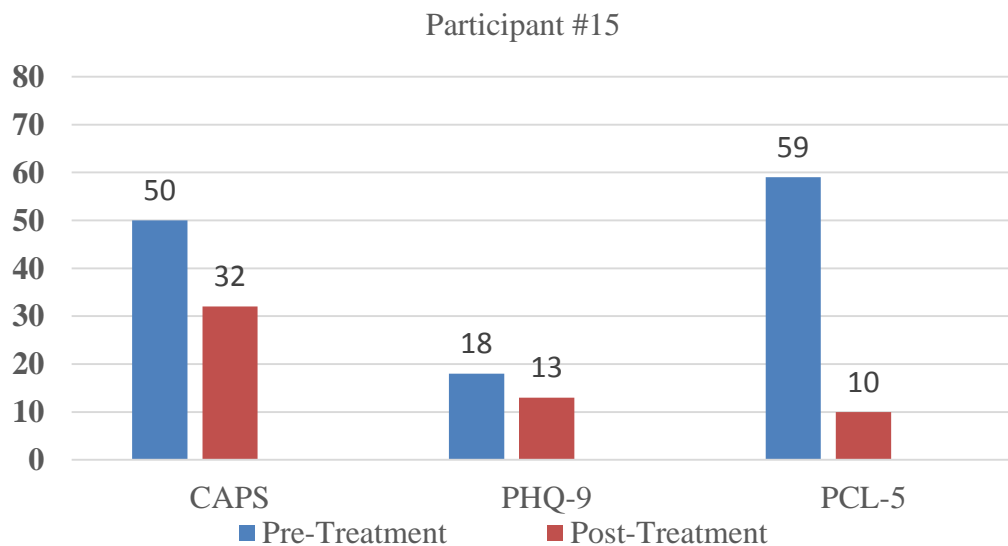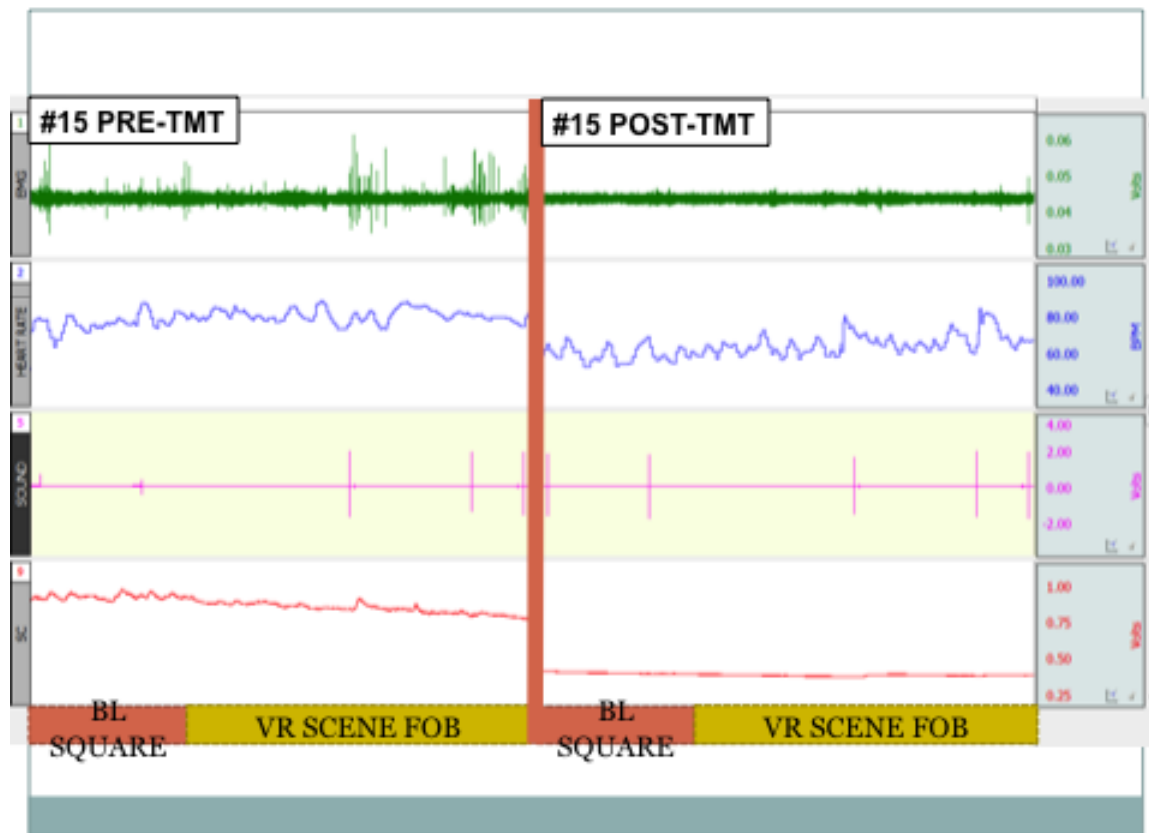
Participant #15

Figure 27. Participant 15 pre-treatment and post-treatment psychophysiological indicators of distress.

Note. From top row to bottom row: EMG, heart-rate, startle, skin conductance.

14. TABLES

Table 1: Comorbid DSM-5 diagnoses as assessed at the pre-treatment assessment

Diagnosis	N
Major Depressive Disorder	9
Panic Disorder	3
Agoraphobia	6
Social Anxiety Disorder	2
Generalized Anxiety Disorder	3
Obsessive-Compulsive Disorder	2
Substance Use Disorder, past 12 months	1
Met for 0 additional diagnoses	6
Met for 1 additional diagnosis	2
Met for 2 additional diagnoses	2
Met for 3 additional diagnoses	2
Met for 4 additional diagnoses	2
Met for 5 additional diagnoses	1

Table 2. Study completers: Paired t-tests examining change in PTSD and depression symptoms.

Outcome	N	M	SD	M Difference	SD Difference	t-Test	P Value	Cohen's d	95% Confidence Interval	
									Lower	Upper
CAPS										
Pre Post	10	42.70 27.90	10.45 15.96	14.80	12.27	3.81	.004	1.21	6.02	23.58
Post 3mth	8	28.28 28.38	17.76 15.56	0.00	10.66	0.00	1.000	0.00	-8.92	8.92
PCL-5										
Pre Post	10	46.40 26.50	15.27 20.87	19.90	18.66	3.37	.008	1.07	6.55	33.25
Post 3mth	8	29.75 35.00	7.88 6.94	-5.25	11.23	-1.322	.228	-0.47	-14.64	4.14
PHQ-9										
Pre Post	8	15.50 11.25	6.23 6.27	4.25	5.15	2.34	.052	0.83	-0.05	8.55
Post 3mth	6	12.00 12.67	6.78 6.38	-0.67	4.32	-0.38	.721	-0.16	-5.20	3.87

Table 3. Treatment completers: Paired t-tests examining change in PTSD and depression symptoms.

Outcome	N	M	SD	M Difference	SD Difference	t-Test	P Value	Cohen's d	95% Confidence Interval	
									Lower	Upper
CAPS										
Pre Post	9	44.33 29.33	9.63 16.23	15.00	13.00	3.46	.009	1.15	5.01	24.99
Post 3mth	7	30.29 29.29	18.29 16.58	1.00	11.11	0.24	.820	0.09	-9.27	11.27
PCL-5										
Pre Post	9	49.89 28.56	11.21 21.04	21.33	19.20	3.33	.010	1.11	6.57	36.09
Post 3mth	7	32.86 36.14	22.11 20.92	-3.29	10.55	-0.82	.441	-0.31	-13.04	6.47
PHQ-9										
Pre Post	7	16.86 12.14	5.30 6.20	4.71	5.38	2.32	.059	0.88	-0.26	9.69
Post 3mth	5	13.40 12.80	6.54 7.12	-0.60	3.36	0.40	.710	-0.18	-3.57	4.77